ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 16, Number 6 NOVEMBER-DECEMBER, 1932 Serial No. 86

A CRITIQUE OF ENDOCRINE THERAPY.*

JOSEPH C. AUB

BOSTON

In the past twenty years, great advances in medicine have occured in our understanding of the glands of internal secretion so that now the accumulation of facts about many of these glands surpasses our understanding of the functions of most other organs of the body. During this period, there has accumulated not only a great mass of physiological knowledge but also brilliant chemical successes which have resulted in the isolation, purification, and even crystallization of many active principles. This work is giving to the clinicians their most powerful therapeutic agents, yet the advances in clinical medicine are seriously lagging behind those in chemistry and physiology. This is somewhat surprising because the natural occurrence of endocrine abnormalities in man offers excellent opportunities for serious study, not only of their subtler functions and interrelations, but also of the effects of substitution therapy. New tests of functional activities and greater knowledge of interrelationships are most sorely needed, but it is particularly substitution therapy that I wish to discuss briefly today.

Certainly, the active principles of the thyroid, parathyroid, islands of Langerhans, posterior pituitary, and adrenal glands are producing dramatic therapeutic results; but some active principles, which have most striking effects in the lower animals often show disappointing results when given to man. What are some of the factors which may be here involved?

Ten years ago, poor results were blamed upon the poor pharmaceutical preparations which were available. These may still be a factor, but they are certainly becoming progressively less so in the best preparations, even though it is highly likely that most of the really active principles are not yet in their true physiological form. Thus, highly purified thyroxine was shown by Swingle (1) to be not nearly so effective as whole thyroid gland when taken by mouth. This certainly indicates a loss of that pharmacological action, which is retained when purification reaches only the thyroxine-polypeptide stage developed by Harington and Salter (2). Adrenaline is said by Szent-Gyorgyi (3) to be a degradation product of a far more potent

*Delivered as the Presidential Address at the New Orleans Meeting of the Association for the Study of Internal Secretions, May 9, 1932.

compound. Probably, no immunity would be produced against parathormone (4) were it completely and exactly the active principle of the parathyroid glands. Examples such as these indicate that the great advances which have been made so rapidly need still further refinement, for our highly purified extracts may be degraded products and may not yet be in the chemical form from which the maximal normal therapeutic results can be obtained.

Surely, we are too impatient and want results too promptly. It should be expected that gradual metabolic changes such as those produced by anterior pituitary gland abnormalities would be influenced but slowly by any replacement therapy. Responses, such as it should produce, cannot occur in man in the course of days and this is particularly true when the time for physiological changes such as take place in the ovaries or bones is long past due. Clinical abnormalities bear the same relation to the usual physiological experiments that chronic diseases bear to acute infections. Correction of them is difficult because they involve complicating secondary, chronic effects upon other bodily structures.

A third essential in therapy is adequate dosage. This factor has been recently stressed by Minot in regard to iron therapy in the anemias. It is surely as important in the treatment of endocrine abnormalities. When a given form of treatment has been undertaken, it should be pushed to a definite physiological response, for diagnostic as well as therapeutic reasons. In diseases of internal secretion, the response to organic medication is far more marked when therapy is needed. This has often been stated before and it has recently been established by much experimental work. Thompson (5) in man and Boothby (6) in dogs have shown that the metabolic response to a given dose of thyroid is greater in a patient with myxedema, and the response becomes progressively smaller as the patient approaches normal. With normal individuals much larger doses of thyroid are required to influence the basal metabolic rate. The same phenomenon may be seen in the effects from parathormone and insulin. Ten or fifteen units of parathormone may produce an increase of the blood calcium in a patient suffering from tetany whereas one hundred units are required to produce an equivalent change in a normal individual (7). A similar, though less marked, relationship exists with insulin injections. This is but another example of homeostasis so ably developed by Cannon (8). It is much easier to bring the human body back to the normal than it is to distort it from the normal equilibrium. This principle is of value in regulating therapy, though it is no excuse for the use of pluriglandular preparations. If a usual dosage of thyroid does not raise a low basal metabolic rate, it signifies to me that the low metabolism is a physiological rather than a pathological phenomenon and that thyroid therapy is usually not indicated. Thus the low basal metabolic rates found in so-called nephrosis are influenced only with very large doses of thyroid. The satisfactory results,

which occasionally follow large therapeutic doses of thyroid, are probably due to some other effect than the elevation of total metabolism.

We judge therapeutic effects by relatively simple laboratory tests, which give no indication of many physiological changes. Indeed, we do not understand many of these changes. For instance, the toxic effects of thyroid may not at all parallel the stimulation of the basal metabolic rate. The basal metabolism may be practically unchanged even though a patient complains of tachycardia, nervousness, diarrhoea, or sleeplessness. Thyroid probably influences nearly all body cells, more or less profoundly. Recent observations made at the Huntington Memorial Hospital give some suggestion of this. In the course of a broad, independent investigation of carbohydrate metabolism, Doctors William T. Salter and Frederick H. Scharles (9) have been studying the amylase content of tumors. During these investigations, they attempted to vary the amylase concentration of cells and have found that in thyrotoxic mice the amylase activity of tumor cells is far higher than in those not injected with thyroxine. Here we have an example of markedly increased activity in a cell enzyme stimulated by injections of a crystalline internal secretion. In this tumor this is particularly interesting since Dr. Ovid Meyer (10) has shown that it does not respond to thyroxine by an elevation of total metabolism as does its host. In other words, this particular sarcoma does not respond to thyroxine by the usual elevation of total oxygen consumption, but it does show a response by a marked increase of an intracellular enzyme. Another analogous example, reported by Page (11) indicated that parathormone, when injected into rats, reduced the concentration of the normal bone enzyme, phosphatase.

These are probably not isolated phenomena. It is most likely that many other examples will be found of endocrine secretions influencing intracellular enzymes. Such discoveries would greatly broaden the realm of this society, for I hope you will agree that intracellular enzymes properly belong with the study of internal secretions. These observations show that the gross indices of therapeutic effects, which we employ at present, give little indication of the subtle change which may actually occur. It is true, therefore, that there are possible unknown dangers associated with large therapeutic dosages. However, until more is known about these phenomena, I think it still remains a satisfactory rule that when endocrine therapy is really needed, a sufficient amount should be given to produce a true pharmacological response.

My final suggestion is not to lay too much stress upon endocrine therapy alone. In abnormalities which are largely metabolic in nature, attention to general principles is often of great importance. For example, in obese amenorrheic patients, reduction in weight alone will often be followed by regular menstrual cycles. As frequently mentioned, removal of foci of infection will often reduce the intensity of hyperthyroidism. Attention to the factors of general hygiene and metabolism, which formerly

were carefully observed in diabetes, are still of value in spite of the great help of insulin.

I have stressed these simple principles because they are so frequently neglected in our modern therapy. In recent years, at many clinical meetings the nihilistic point of view in regard to treatment has been actively championed. This point of view did much good by eliminating what was false and unproved, and an "intelligent scepticism" (12) is always most valuable, but the reaction has gone too far: it has too often engendered the remark "nothing is known about that," when the statement should have been "I know nothing about that." The former remark is a pessimistic admission of defeat; the latter a challenge to investigate, to study the literature, and to utilize what is to be found therein. It is obvious in which direction lies progress.

REFERENCES

1. Swingle, W. W., O. M. Helff and R. S. Zwemer: The effect of thyroxin and its acetyle derivative on amphibians and mammals. Am. J. Physiol. **70:** 208. 1924.
2. Harington, C. R. and W. T. Salter: The isolation of l-thyroxine from the thyroid gland by the action of proteolytic enzymes. Biochem. J. **24:** 456. 1930.
3. Svirbely, J. L. and A. Szent-Gyorgyi: Function of the adrenal medulla, Nature, April, 1932.
4. Albright, F., W. Bauer, M. Ropes and J. C. Aub: Studies of calcium and phosphorus metabolism. IV. The effect of the parathyroid hormone, J. Clin. Investigation, **7:** 139. 1929.
5. Thompson, W. O., P. K. Thompson, A. G. Brailey and A. C. Cohen: The calorigenetic action of thyroxin at different levels of basal metabolism in myxedema J. Clin. Investigation, **7:** 437. 1929.
6. Boothby, W. M. and C. M. Wilhelmj: Comparison of the effect of single intravenous injections of thyroxine before and after thyroidectomy. Am. J. Physiol. **97:** 506. 1931.
7. Aub, J. C., F. Albright, W. Bauer and Elsie Rossmeisl: Studies of calcium and phosphorous metabolism. VI. In hypoparathyroidism and chronic steatorrhea with tetany with special consideration of the therapeutic effect of thyroid. J. Clin. Investigation, **11:** 211. 1932.
8. Cannon, Walter B.: The Wisdom of the Body, W. W. Norton & Co., New York. 1932.
9. Scharles, F. H. and W. T. Salter: Influence of hormones on a glycogen-splitting enzyme in malignant tissue. J. Clin. Investigation, **11:** 830. 1932.
10. Meyer, O. O., C. McTiernan and J. C. Aub: The effect of thyroxin upon the metabolism of isolated normal and malignant tissue. J. Clin. Investigation, **11:** 821. 1932.
11. Page, I.: Effect of parathormone on phosphatase, Biochem. Ztschr. **223:** 222. 1930.
12. Christian, H. A.: The Practitioners need of an intelligent skepticism, New England: J. Med. **202:** 1181. 1930.

JUVENILE OBESITY

HUGO R. RONY, M.D.
From the Endocrine Clinic, Department of Medicine, Northwestern University Medical School
CHICAGO

The rôle of endocrine disturbance in the etiology of obesity is far from being clearly understood. Some observers, for example Newburgh (1), pay little or no attention to this phase of the problem and apparently feel that glandular disorders are unimportant as primary causative factors in obesity. Others (2) consider obesity in a majority of cases to be on an endocrine basis.

There are probably many reasons for this divergence in viewpoint, but the following two are worthy of special mention: (1) In obese adults definite evidence of glandular disturbance such as low basal metabolism, or amenorrhea is rare. Suggestive evidence in the history such as rapid gain in weight after child birth or in the climacterium, or physical findings such as anomalies in hair distribution, or tonus changes of the vegetative nervous system, or slight disturbances of menstruation, etc., is very common; however, the use of such findings as criteria for the diagnosis of endocrine disorders and particularly the interpretation as to the gland or glands involved is largely a matter of opinion. (2) Even in the presence of manifest and unquestioned endocrine disorders the proof of their etiological relationship to obesity is open to question.

Both these difficulties are materially reduced when one concentrates his attention on the juvenile age which provides a highly sensitive test period for glandular influences due to the known marked effects of the glands on the somatic, sexual and mental development. In the developmental period endocrine disorders, especially of the pituitary and sex glands, and to some extent of other glands, are relatively easily recognized and readily identified, whereas in adult life the influence of these glands on development has waned. We believe that results reached in an analysis of juvenile obesity are essentially applicable to adult obesity also.

Fifty unselected cases of obesity in childhood and adolescence were studied. These cases included those of 22 boys and 28 girls between 7 and 18 years of age. The average age was 13½ years. The excess weight varied between 25 per cent and 128 per cent of the normal average weight; the average excess weight was 54 per cent.

The study of these cases consisted in obtaining a careful history, taking measurements and making observations pertinent to growth, sexual and mental development. In addition the basal metabolism and the sugar tolerance were determined in most cases, and x-ray pictures of the sella turcica taken in many cases.

Family History: Special attention was paid to the occurrence of obesity, diabetes and mental disturbances in the family. In the 42 cases in which reliable information was available, obesity of the father or mother or both was mentioned in 24 cases, while in 18 cases obesity in the family was absent. Diabetes of the parents could not be traced in any case. In one case a grandmother, in another case a half-sister had severe diabetes. Feeblemindedness or insanity in the family was mentioned in eight cases. In one case the mother had suffered from paralysis agitans.

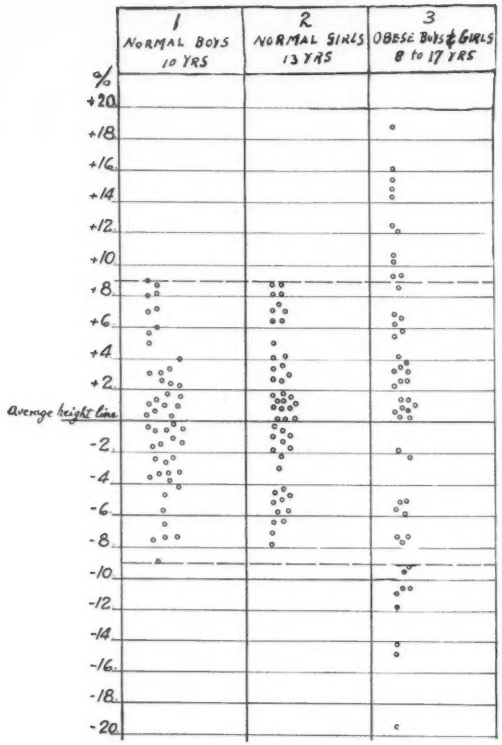
Duration: In more than half of the cases (32) the patients had been markedly overweight since infancy or early childhood. In one of these cases a fracture of the hip, in another infantile paralysis were mentioned as being followed by additional gain in weight. Hereditary syphilis was present in one case. In 18 cases it was definitely stated that prior to the onset of obesity the patients were underweight or of normal weight. This occurred at the age of five in two cases, at six in two, at eight in one, at nine in two, at 10 in two, at 11 in four, at 12 in four, and at 15 in one of these cases. Tonsillectomy just preceding the onset of obesity was mentioned in four cases, appendectomy in one case. In another case, an 18-year-old girl, with the onset of obesity at 15, it was noticed that the child stopped growing at the same time. In the remaining 12 cases, except for a healthy appetite which, however, was present in all cases except one, the history did not give any suggestion as to possible etiologic factors.

Height: To compare the height of our subjects with the height of normal boys and girls of the same age we used Boas and Wissler's data (3), which are based on measurements of thousands of school children in Worcester, Mass.; Toronto, Canada; and Milwaukee, Wis. According to these authors the average variation from the calculated average height in all the groups of boys and girls between 8 and 17 years of age was ± 8.9 per cent.

In Table I, columns 1 and 2 show the individual height variations, cited by these authors, in two representative groups of 50 school children each, as compared with the average height of the entire group. Their data show that the height varies between 9 per cent above and 9 per cent below the average height. Column 3 shows the height variations of our 50 obese juveniles as compared with the calculated average normal height of each individual. It is seen that the range of variation is greatly extended in both directions: there are heights 19.2 per cent above and 19 per cent below the corresponding normal height, the total variation being ± 19.1 per cent. There are 11 subjects in our group who are more than 9 per cent taller, and eight subjects who are more than 9 per cent shorter than their normal average height. These 19 subjects, more than one-third of those studied, registered heights entirely outside of the variations seen in normal children of the same ages.

Sexual Development: Marked retardation of sexual development as evidenced by undescended or undersized testicles, undersized penis, lack

TABLE 1



of pubic hair, amenorrhea, underdevelopment of mammae in girls above 14 years of age, etc., was noticed in 24 cases. Precocious puberty occurred in 3 cases. Twenty-three patients showed apparently normal sexual development; however, several of these were girls under 14 years, whose sexual development cannot be adequately evaluated at this age.

Mental Development and Nervous System: There were eight cases of feeblemindedness with the Intelligence Quotient ranging between 35 and 72. One of these patients exhibited signs of cerebral palsy, had occasional epileptiform attacks and, without apparent cause, subfebrile temperature and rapid pulse; one had hemihypertrophia facialis; two complained of insomnia, frequent headaches and enuresis. Of the mentally normal children one showed sequelae of infantile paralysis and had chronic subfebrile temperature. The nervous system and the mental development in the remaining cases were normal.

Sella Turcica: Roentgenographic studies were obtained in 24 cases. In 17 the sella was described as "normal in size and outline," in one case it was "extremely small," in three cases "small," in two cases "rather large and deep," and in one case "the sella and whole aspect of the skull

is that of acromegaly." Calcification of the pineal body was not found in any case.

Basal Metabolism: Satisfactory readings were obtained in 42 cases. The B. M. R. was within ±10 per cent in 22 cases; between —10 per cent and —15 per cent in four cases; between —15 per cent and —20 per cent in eight cases; below —20 per cent in two cases; none below —23 per cent. A rate above +10 per cent was obtained in six cases, none exceeding +13 per cent. The tendency toward low basal metabolism becomes still more evident if the basal metabolic "ratios" instead of rates are calculated (4).

Sugar Tolerance: In each case 100 grams of glucose in 500 cc. of water was given on an empty stomach. The test was successfully carried out in 46 cases. Normal blood sugar curves were obtained in 21 cases. Definitely high sugar tolerance in repeated tests was found in 17 cases. Low sugar tolerance, the blood sugar exceeding 200 mgm. one to two hours after ingestion and failing to return to the initial value after three hours, was found in repeated tests in eight cases; five of these showed glycosuria at some time during the test.

TABLE 2
RESUME OF DATA

Growth.....	Deficient—9			Excessive—11			Normal—30	
Sexual development	Deficient 6	Excessive 1	Normal 2	Deficient 5	Excessive 2	Normal 4	Deficient 13	Normal 17
Mental deficiency...	2	..	1	..	..	1	2	2
Sugar tolerance.....	Low 1 High 3	Low .. High 1	Low 1 High 1	Low 1 High ..	Low 1 High ..	Low .. High 1	Low 2 High 4	Low 3 High 6
Low B.M.R. (below —15%).....	..	..	1	..	1	2	2	4
All tests normal.....								6

Table 2 is a résumé of the more important data. It is seen from the table that the growth was normal in 30 cases. Seventeen of the 30 subjects were also normally developed sexually. Nine of these 17 showed abnormal sugar tolerance, including four with a low basal metabolism. There were only six out of the 50 cases which proved to be normal in every test carried out.

DISCUSSION

From the study of these 50 cases and the tabulation of the results of the tests carried out, two features draw attention. One is that *some* abnormality was found in not less than 44 cases, 88 per cent of the total. This high incidence of abnormal findings in juvenile obesity is the more striking since only comparatively simple tests were employed in this study.

The second feature is that the abnormalities found in this series comprise variations from the normal in *both* directions. Thus there are cases with accelerated and others with delayed somatic development; cases with sexual infantilism and others with precocious puberty; the sugar tolerance is abnormally high in some cases, and abnormally low in others. Furthermore, all possible combinations of these variations exist in certain of the cases.

Before we comment on these two peculiar features it will be necessary to attempt an interpretation of these anomalies as glandular disturbances. This is a difficult task in view of the ambiguity of our present criteria. However, it is possible to make some statements with a fair degree of reliability.

Growth and Sexual Development: In interpreting the anomalies of growth and sexual development etiological factors other than glandular must be excluded. Two such cases were found in this series. One was a case of stunted growth, particularly of the legs, following infantile paralysis, apparently due to disuse. The other was a case of achondroplasia, a disturbance of bone growth which may or may not be of glandular origin Rickets or other non-glandular diseases were not observed in any case in this series.

After exclusion of such cases, the problem is to identify the gland or glands involved. The anterior lobe of the pituitary gland, the sex glands, the adrenal cortex, the thyroid, and possibly in rare instances, the parathyroids and the pineal body must be considered. It is generally recognized that most disturbances in growth or sexual development when due to endocrine disorder are primarily of pituitary origin. However, in some cases this gland may not be involved or its involvement may be secondary to other primary endocrine dysfunction.

In the following classification "total" designates involvement of both the growth and sex-promoting apparatus of the anterior lobe of the pituitary; "partial" means the affection of either one.

(a) The occurrence of deficient growth and sexual under-development was classified as total hypopituitarism: 6 cases.
(b) Excessive growth and precocious puberty, as total hyperpituitarism: 2 cases.
(c) Deficient growth and normal sexual development, as partial hypopituitarism: 2 cases.
(d) Excessive growth and normal sexual development, as partial hyperpituitarism: 4 cases.
(e) Deficient growth and precocious puberty, as dyspituitarism: 1 case.
(f) Excessive growth and sexual underdevelopment, as either dyspituitarism, or primary hypogonadism with secondary hyperpituitarism: 5 cases.
(g) Normal growth and sexual underdevelopment, as either partial hypopituitarism, or primary hypogonadism: 13 cases.

On the basis of clinical observation and the tests employed, it is impossible to decide which one of the two diagnoses offered in the categories (f) and (g) is correct. Furthermore, it is possible that in the cases of

the groups (b) and (e) the pituitary disturbance is secondary to a primary adrenal hyperfunction. However, in view of recent knowledge concerning the importance of the pituitary sex-promoting hormone for sexual development, it is safe to say that most or all of these cases represent primary or secondary pituitary disturbance. Accordingly, we find that 33 cases in our series show some disturbance of the pituitary gland; in some of these cases this disturbance may be secondary to sex gland or adrenal dysfunction.

Basal Metabolism: Ten cases were found with basal metabolic rates less than —15 per cent. Of the various conditions capable of causing moderately low basal metabolism primary hypothyroidism, hypothyroidism secondary to hypopituitarism, and abnormal basal metabolism of central origin (5) had to be considered. Only one of our subjects showed the typical clinical picture of juvenile hypothyroidism, a 14-year-old girl, slightly underdeveloped, mentally subnormal, with dry skin, coarse hair, poor teeth, etc., and a marked response to thyroid therapy. This case was classified as primary hypothyroidism. There were two mentally subnormal subjects with low basal metabolism who did not show other signs of hypothyroidism and did not respond to thyroid therapy. In both cases insanity in the family was revealed in the history; in one case hereditary syphilis was present. Both subjects showed signs of hypopituitarism. The other seven subjects with low basal metabolism were mentally normal. Three of them belong to the hyperpituitary group, four to the group without endocrine disturbance. In all these cases the low basal metabolism is probably of central origin. In five additional cases of mental subnormality the basal metabolism was within the normal limits and other suggestive signs of hypothyroidism were absent.

Accordingly, primary hypothyroidism is rare in juvenile obesity. This is in accordance with previous findings in the study of adult obesity (4).

Sugar Tolerance: Abnormal sugar tolerance is usually considered as a manifestation of some endocrine disturbance. The pituitary gland and the pancreatic islets especially, but also other glands appear to have a functional bearing on sugar tolerance.

Pituitary gland hypofunction is said to be associated with high sugar tolerance, hyperfunction with low sugar tolerance. In this series, however, no consistent relation was observed as is evident from Table 2. The following examples will illustrate this.

C. L., a 14-year-old boy, obese since infancy, weighed 181 pounds (39 per cent overweight). His height was 66¾ inches (6.8 per cent above average height). He was mentally normal. He had had precocious puberty. X-ray examination of the skull was suggestive of acromegaly. The B. M. R. was —22 per cent. Sugar tolerance showed: initial value, 87 mgm.; after one hour, 116 mgm.; after two hours, 109 mgm.; after three hours, 87 mgm. In this instance signs of hyperpituitarism are associated with low basal metabolism and high sugar tolerance.

B. O., a 16-year-old girl, obese since infancy, weighed 180 pounds (110 per cent overweight). Her height was 58 inches (9.4 per cent below average height).

She had not menstruated. The sexual organs were infantile. She was feeble-minded with occasional epileptiform attacks. The sella was normal. The B. M. R. was +11 per cent. Sugar tolerance showed: initial value, 95 mgm.; after one hour, 266 mgm.; after two hours, 308 mgm.; after three hours, 266 mgm., with glycosuria during the test. In this instance signs of hypopituitarism are associated with low sugar tolerance.

Furthermore, abnormal sugar tolerance, high or low, was found in several cases without any indication of pituitary disturbance. (Table 2.)

The sugar tolerance in relation to the pancreatic islets in juvenile obesity is of particular interest in view of the problem of the relation of obesity to diabetes. It is known that in the adult obesity frequently precedes diabetes. Joslin (6) explains this by assuming that a high carbohydrate intake, a frequent habit of obese persons, constitutes undue strain for the islets, which are later exhausted, resulting in diabetes. Falta (7) goes even farther and claims that many cases of obesity are primarily due to hyperinsulinism which later, because of the undue activity of the islets, leads to their early exhaustion, and diabetes. These views would explain the higher incidence of high sugar tolerance in juvenile obesity as compared with adult obesity (Table 3). However, it is difficult to reconcile with these views the occurrence of low sugar tolerance in a not negligible percentage of cases. These obese children with low sugar tolerance continue to gain weight, and have not yet developed diabetes. This corresponds with the old observation that diabetes is rare in obese children. We doubt whether low sugar tolerance in juvenile obesity indicates primary pancreatic disturbance. It is known that low sugar tolerance may be of cerebral origin (8). It seems significant that four of our cases with low sugar tolerance, out of eight, belong in the mentally deficient group.

TABLE 3
SUGAR TOLERANCE IN OBESITY

	Adults	Juveniles
Number of cases	70	46
Normal sugar tolerance	63%	45%
High sugar tolerance	14%	36%
Low sugar tolerance	23%	18%

These results indicate that there is no strict relationship between sugar tolerance and glandular disturbance in juvenile obesity. Other factors, cerebral particularly, must also be considered.

We find, then, that disturbances of the pituitary gland (and gonads), low basal metabolism without hypothyroidism, anomalies of carbohydrate tolerance, and mental deficiencies are frequently associated with juvenile obesity. What is the significance of these anomalies as to the etiology of the obesity?

(a) It cannot be simply chance coincidence; these anomalies are much too frequent as to support this possibility.

(b) Direct etiological relationship can hardly exist for the following reasons: In the first place none of these different types of anomalies was found in every case. Disturbances of the pituitary-gonad system were the most frequent, but even these were entirely missing in 34 per cent of the cases. Furthermore, in 12 per cent of the cases no abnormality whatsoever was found. Finally, and most peculiarly, the anomalies found represent deviations from the normal in both directions inasmuch as in some cases hypofunction and, in others, hyperfunction was found. We may add here that similar functional states of the same gland are known to be associated with either obesity or normal weight or leanness. Thus, the hypopituitary adult is frequently obese, but one type of hypopituitarism (Simmond's) is characterized by extreme emaciation. Low basal metabolism and other evidences of hypothyroidism may be associated with obesity or with leanness.

(c) The endocrine, metabolic and mental abnormalities may be but indicators of the presence of some other disturbance common to all cases, this latter being the direct cause of the obesity. The nature and location of this common disturbance must then be such that it should be likely to occur simultaneously with any of the anomalies found without itself being caused by them. There is experimental evidence that the hypothalamus (tuber cinereum) contains structures instrumental in fat deposition. Smith (9) has shown that the whole pituitary gland can be removed in rats without definite effect on weight if care is taken not to injure the adjacent brain tissue; however, if the tuber cinereum is destroyed, extreme adiposity will follow. Wertheimer (10) found that accumulation of fat in the liver known to occur in phloridzin poisoning can be prevented by severing the spinal cord in the cervical region, thus showing the importance of nervous factors in fat mobilization. Grafe and Gruenthal (5) proved on dogs that injury to certain parts of the hypothalamus is regularly followed by a decrease of the basal metabolism. In addition it has been suggested on the basis of clinical observation (4) that the body fat level of normal persons is maintained by the operation of a regulatory mechanism which is chiefly of nervous nature. It was concluded that, in analogy with heat regulation, an automatic reserve fat regulation must exist with a nervous center which controls the primitive impulses for caloric intake (appetite) and caloric output (muscle activity) as well as all other factors of the caloric equilibrium. Furthermore, it was asserted that in obesity, due to some disturbance in this central control, the regulatory mechanism is adjusted to an abnormally high body fat level, although it operates with normal efficiency. In view of the experimental evidence mentioned above, it was suggested that the center of this regulatory mechanism is located in the hypothalamus. Such a center would naturally have close embryological, anatomical and, possibly, functional relations with the pituitary gland, with other metabolic centers in the midbrain, and certain structures of the brain. It would be likely that a simultaneous occurrence of dis-

turbances of some or all of these structures may take place frequently without one necessarily causing the other.

On this basis the following interpretation of our findings in juvenile obesity is offered: Subjects of juvenile obesity which are otherwise entirely "normal"—12 per cent in our series—are due to developmental anomaly limited strictly to the reserve fat regulating center, resulting in a disturbance of the primitive impulses for caloric intake and output with shifting of the body fat level, without glandular or metabolic changes. If the developmental anomaly also includes related structures in or near to the hypothalamus, then the various "pathological" forms of obesity will result, such as those with pituitary or cortical manifestations or with abnormal basal metabolism or abnormal carbohydrate tolerance. Neither of these anomalies has causative relation to the obesity. They signify only the involvement of symptom-producing areas in addition to the disturbance of the otherwise "silent" fat reserve center.

SUMMARY

The juvenile age constitutes a sensitive test period for the detection and identification of glandular disturbances, due to the known marked effects of the glands on somatic, sexual and mental development. Fifty unselected cases of obesity in childhood and adolescence were studied for the possible rôle of endocrine disturbances in the etiology of obesity. The study included history, clinical examination, measurements pertaining to growth, sexual and mental development, basal metabolism, sugar tolerance, and x-ray pictures of the sella turcica.

Disturbances of the pituitary and sex glands, moderately low basal metabolism without hypothyroidism, abnormal sugar tolerance, and mental deficiencies are frequent findings in juvenile obesity. Only six of the fifty cases studied showed no abnormal findings in at least one of these fields. However, the anomalies found represent deviations from the normal in both directions inasmuch as in some cases hypofunction and in others hyperfunction of the same gland was found. This along with other observations strongly suggests that there is a relationship between endocrine anomalies and obesity, but it is not of etiological nature.

The etiology of obesity, juvenile or adult, "exogenous" or "endogenous" is apparently uniform: it is a disturbance of the mechanism that regulates the body fat content, and is probably hypothalamic in origin.

REFERENCES

1. Newburgh and Johnston: Ann. Int. Med. **3**: 815. 1930.
Tileston: In Barker's Endocrinology and Metabolism, Vol. 1, P. 37. New York. 1922.
2. Zondek: Die Krankheiten d. endocr. Druesen. Berlin. 1926. P. 130.
Bernhardt: Zentralbl. f. inn. Med. **52**: 1170. 1931.
3. Boas and Wissler: Ann. Rep. of the Dept. of Int. **1**: 25; 108. 1904.
4. Rony: Ill. Med. J. **59**: 302. 1931.
5. V. Grafe: Ergebn. d. Physiol. **21**: (Part 2), 1. 1929.
6. Joslin: Treatment of Diabetes Mellitus. Lea & Febiger, Philadelphia. 1928.

7. Falta: Wien. klin. Wchnschr. **43**: 289. 1930.
8. Folin, Denis and Smillie: J. Biol. Chem. **17**: 519. 1914.
Cannon, Shohl and Wright: Am. J. Physiol. **29**: 280. 1911.
9. Smith: J. A. M. A. **88**: 158. 1927.
10. Wertheimer: Pflueger's Arch. f. d. ges. Physiol. **213**: 262. 1926

SOME OBSERVATIONS ON ANTERIOR LOBE HYPERPITUITARISM

J. K. FANCHER, M.D.
ATLANTA, GA.

The condition of gigantism, while relatively rarely observed and recorded in the literature, has its origin in conditions which are serious at best, and usually fatal. Though the diagnosis is easy, the usual therapeutic methods are unsatisfactory even in the incipient cases where treatment aims to be preventive. Broadly speaking, two general types may exist, i.e., the proportionate or typal and the disproportionate or non-typal. The first is very rare* and usually the recorded cases fall into the second group. These are characterized by overgrowth, most marked in the extremities, with or without acromegalic changes, with juvenile or normal genitalia, and a tendency to marked hypertrichosis.

According to Lisser (2), the condition is one of abnormal tallness; originating in childhood, and continuing to develop into adult life until epiphyseal closure prevents further growth; due principally to an accelerated secretion of the growth accelerating hormone of the anterior lobe of the hypophysis; and secondarily dependent on a delayed epiphyseal closure due to insufficiency of the gonads, which permits growth of long bones to continue at an age when growth should have ceased. Pathologically the state shows adenomatous hyperplasia of the anterior lobe of the pituitary, followed by sclerotic or cystic degeneration paralleled by similar changes in other incretory structures. Clinically, the excessive height (from 6 feet 6 inches to 8 feet or even more), with marked disproportion of the extremities to body length, the frequent enlargement of the sella turcica, possible acromegalic changes, hypertrichosis, abnormalities in carbohydrate metabolism, and a progressive course from initial hypermetabolism to terminal hypometabolism, are among the more characteristic features.

In addition, in several of our patients, a peculiar mental attitude has been manifest, basically an inferiority complex from the realization of their abnormalities. They are irritable and antagonistic, sullen and sometimes hard to control; another expression is found in a period of self-exaltation in which they are proud of their abnormality. The mental attitude tends to improve with the cessation of growth.

The gravity of the prognosis in gigantism is shown by the statistics of mortality. In 1900, the average age of mortality (3) was 21.3 years, and in some of these cases the abnormality did not show itself until the age of prepubescence. Early diagnosis is important, as has been stressed by Englebach (4) and others. In Sutton's case (5), prompt improve-

*Bassoe(1) denies its existence.

ment followed opotherapy, but the multiglandular therapeutic approach (thyroid and ovarian substance) clouds the picture.

Present-day treatment of overgrowth is varied. It consists of:

(1) X-ray or radium therapy with which some good results have been reported. A hypofunctional level requiring treatment is usually produced.

(2) Surgery. This is advisable in tumor cases.

(3) Anterior lobe extract. Need for this therapy comes only late in the disease when destruction and atrophy are advanced and the primary damage is done. In general, the use of other gland extracts has not been advocated. Recently, thyroid extract in conjunction with x-ray treatment, has been tried out (6).

In a series of 2000 cases, at the Good Samaritan Clinic, we have seen ten cases of overgrowth. The subjects were not all giants, according to the adult standard of 76 inches or over, but since therapy must be prophylactic, they were considered to be potential giants. The tallest subject (No. 1296) was 6 feet 5½ inches at 12 years; at 14 years he was 7 feet 6 inches; and at 16 years he was over 8 feet tall (Fig. 1). During the past

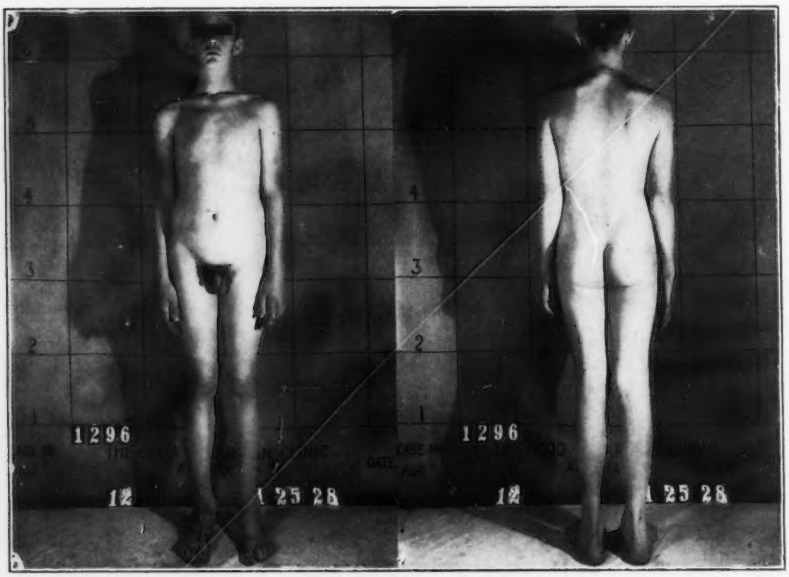


Figure 1

three years, eight cases of overgrowth, or potential gigantism, have been placed on opotherapy alone. All were benefited. Four cases are here reported, two from clinic records, and two from private practice. For comparison, an uncontrolled case also is given.

Considering gigantism, or overgrowth, as primarily anterior lobe hyperpituitarism, from a purely experimental viewpoint we have admin-

istered ovarian substance in the female and orchitic substance in the male to ascertain if an antagonistic action could be demonstrated. The activity of orchitic substance as now prepared is still questioned. Its chief value, if any, should be during pre-adolescence and adolescence (7). After adolescence, most observers agree that it is of little value. Ovarian preparations, on the other hand, are used at nearly all ages. In this series, no untoward effects of any kind have been noted. A brief discussion of the case protocols will serve to illustrate the thesis.

Case 1296 (Unrestrained Overgrowth). The patient was a boy, 12 years of age, complaining of over-development which had begun at the age of 9 and had followed a progressive course. He was delivered normally at term, the birth weight being 9½ lbs.; he was breast fed for eighteen months. His first tooth appeared at ten months and he walked and talked at the age of a year. The history records measles, mumps, pertussis, tonsillitis and grippe; his tonsils had been removed the previous year. At the time he entered the Clinic he weighd 200 lbs. His actual height was 77.5 in. (normal prediction 58 in.). He had an arm reach of 78.8 in., and a torso length of 38.5 in. The circumference of the head was 23 in. He showed a normal temperature of 98.6 and a slightly rapid pulse rate of 92. The thyroid was soft and uniformly enlarged; the pubic hair was feminine in type; the genitalia were juvenile; he was knock-kneed and the arms, legs, hands and feet were disproportionately long in relation to the body. The orthodontic report showed small lateral incisors, wide spacing of the upper central incisors and upper and lower cuspids with an apparent overgrowth of both arches. Radiologic study showed a greatly enlarged sella and open epiphyses. The Wassermann test was negative. On a diagnosis of gigantism, x-ray therapy was advised and the patient took five treatments. He developed headache and loss of hair, and this led to refusal of further treatment. Since this time his growth has continued at a rapid rate, and now at the age of 16 years, he is over 8 feet tall. This case is presented for comparison with the four other cases in which an experimental opotherapy was followed consistently.

Case L. A. This patient was a boy of 17 at the time he was first seen. He reported a steady growth since about the age of 14. His had been an instrumental delivery; he was said to have been two weeks overtime and to have weighed 8½ lbs. at birth. He walked and talked at the age of one year. The medical history includes measles, pertussis, and influenza in infancy, frequent sore throat, and the removal of tonsils and adenoids at the age of seven. During the past few years he has been much taller than lads of his own age, which has led to his becoming the butt of their jests; because of this a definite inferiority complex has developed leading him to be very sensitive and irritable. At the time of the examination, the body temperature was 98.6, the pulse rate 88. His weight was 157.8 lbs., and his height was 76 in. (normal prediction 68 in.). He had an arm reach of 78 in. The torso length was 35 in. The contour of the body was masculine. The skin was soft and warm. The eyebrows tended to meet, but the pubic hair showed feminine distribution and there was no body hair. The hands and feet were very large. The thyroid was not enlarged, and the genitalia were of average size. Radiologic study showed an average sized sella and open epiphyses. The basal rate was within the normal limits. The boy did not concentrate or want to study, but had shown definite talent in drawing and had won several prizes with posters which he designed. He was very self-conscious. A diagnosis of potential gigantism was offered, and after a preliminary rest period for the space of a month—designed to give a rough index of the growth rate, which was found to be 1.5 in. per month—he was placed on orchitic substance by mouth and at a level of 185 grains (expressed as fresh substance) per day. With the inception of the opotherapy the growth was checked and epiphyseal closure followed in the course of the next four months, at which time the opotherapy was discontinued. When seen two years later, no further growth was demonstrable.

Case E. P. This patient was a boy of 16 years of age, adjudged to be intelligent. He was the first child of his parents, born at full term without instrumentation, and with a birth weight of 8 lbs.; the mother was very ill at time of delivery and the patient was a "twilight sleep" baby. There was a family history of definite tallness in the male members on both sides of the family, and

the mother reports that the patient was a "long baby." There is a record of a mild attack of varicella at the age of 9, mild pertussis and severe measles during the next year, a suspected parotitis, and two mild attacks of influenza; there were frequent attacks of tonsillitis until a tonsillectomy at the age of six, at which age he also developed mild headaches, which have persisted up to the present time. At the age of 11 he was knocked down by a motor car, but no fractures or loss of consciousness were reported. His sudden growth began between the ages of 10 and 12, and has been constant from that time, the growth having been 0.3 in. in the preceding month. His temperature was 98.6, with a pulse rate of 80. He weighed 149 lbs., was 75.4 in. tall (predicted normal 67 in.). His arm reach was 78.8 in., and the torso length was 37.3 in. The head was large, the lips full and red, and there was a slight overbite with a long and prominent mandible. The orthodontic examination showed the upper set of incisors to be large and long, but without separation. The eyebrows showed a tendency to meet, and there was a moderate hypertrichosis on the distal aspects of the extremities; the pubic hair was of feminine type. The hands, fingers, toes, arms and legs were definitely elongated. The urine, blood, Wassermann, and Goetsch tests were all negative; the radiographs showed a large sella and open epiphyses. The basal metabolic rate was 5 per cent above prediction. A diagnosis of potential gigantism was made and the patient was placed on orchitic substance, 600 grains (expressed as fresh substance) per day. With the inception of the opotherapy further growth stopped. The patient has been under observation for five months; the epiphyses are closing. The case is still under treatment and observation.

Case 1911. This patient was a boy of 14, complaining of overgrowth, irritability, and nervous and emotion instability. The birth history records him as a full-term child, weighing 6½ lbs., and with a length of 22 in. The history further adds that the "head was born five hours before the torso," and that he sustained a birth injury in a "swollen area on the head," which gradually disappeared. His overactive growth period apparently followed an attack of influenza at the age of eighteen months, and has been progressive since that time. He has had a severe attack of measles, frequent epistaxis, and in addition, pertussis, varicella and influenza. Tonsils and adenoids were removed at the age of three, and on three occasions antitetanus serum had been administered. The body temperature was 98.8; the pulse rate 82. The boy weighed 117 lbs.; he had a height of 70.6 in. (predicted normal 61 in.). His arm reach was 71.8 in., and the torso length was 23.5 in. The head circumference was 20.8 in. The skin was warm and soft. The body contour was masculine, and the genitalia were proportionately normal. The limbs were unusually long and the hands and feet were long. The mandible was elongated. The heart was enlarged to the midclavicular line. The thyroid was not palpable. The hair on the vertex was fine, moist and straight. There was a slight growth in the axillae, and the pubic hair was feminine in distribution. The orthodontic report records that the boy was treated during childhood for deficient arch width, and the present condition indicated marked increase in dental arch growth. Eye, ear, nose, throat, neurological, and mental findings were all normal. The urine, blood and Wassermann were normal. X-ray examination of the sella showed slight enlargement; the epiphyses were open. A basal metabolic rate of +21 per cent was recorded. A diagnosis of potential gigantism was offered, and the patient has been treated for the past four months with orchitic substance, 425 gains (expressed as fresh gland), per day, with no increase in height noted.

Case 1877. This patient was a boy of 14, complaining of overgrowth, nervousness and irritability. He was a full-term baby, "born feet first," weighing 10.8 lbs. He was breast fed. The first tooth appeared at six months, and he walked at 13 months. An attack of diarrhoea at the age of 3, tonsillectomy a year and a half later, and pertussis were recorded. At the time of examination the temperature was 98.8, and the pulse rate 80. The patient weighed 142.5 lbs. (Normal prediction 99 lbs.), and he was 73.8 in. tall (normal 61 in.). The arm reach was 75 in.. and the torso length was 35.5 in. The head circumference was 23.3 in. The skin was warm. The body showed masculine contour, with average genitalia and long and slender extremities. The hair on the vertex was fine, soft and straight, the pubic hair was feminine in type. The thyroid was found to be slightly firmer than normal. An orthodontic examination showed four fillings, a malocclusion local in origin and delayed eruption of the first upper right and second premolar. Neurological and mental findings were normal, as were the urine, blood and Wassermann test findings. An unsatisfactory basal rate was reported as —4 per cent. Radiological study showed a large sella and

open epiphyses. A diagnosis of potential gigantism was offered and experimental treatment with whole ovary initiated, 180 grains (expressed as fresh gland) per day. In the past four months the patient has grown less than 3/10 in.

These cases reported show the following characteristics: The mentality is above the average. The span exceeds the height. The rapid growth begins usually between 6 and 14 years. The average birth weight is above 8 pounds (also there is difficult or prolonged labor, instrumentation, or the mother is quite ill before delivery). The average pulse rate is over 80. The sella is of average size or large—never small; the epiphyses are open. The teeth are well formed and widely spaced. Temperature is slightly increased. The basal rate is usually plus. Acromegalic signs, such as large hands and feet, lengthened mandible, large sinuses and hypertrichosis, may or may not be present. No tufting of the terminal phalanges has been noted as characteristic in this series.

The rôle of the gonads in gigantism is little understood. For some time it has apparently been agreed that there is some relationship between the pituitary and the gonads. Teel and Cushing (8), in their experimental gigantism in dogs, reported a loss of libido associated with a varying amount of atrophy in the testes, which was sometimes extreme. Evans (9) has shown that the growth-promoting and the sexual-stimulating hormones of the anterior pituitary are separate and distinct in their action. The male hormone has been prepared in crystalline form by Butenandt (10), who gives it the formula C_{16} H_{26} O_2. This compares closely with the formula for the female sex hormone of Doisy (11), which is expressed as C_{18} H_{22} O_2.

The use of gonadal extracts in our cases is suggestive of an influence toward retarding growth. It is difficult to explain these results solely by coincidence. In some of our cases (not reported here because of incomplete records or for lack of cooperation), growth ceased on giving, and was renewed on omitting treatment. The last case is included because of a suggested influence of ovarian substance upon the male. Extensive work is necessary before any conclusion is warranted. From the results in this series of cases, we feel that the possibility of growth influence through the use of active gonadal preparations warrants further investigative study.

SUMMARY

The serious and fatal condition of gigantism is reviewed and the treatment discussed. Therapy must be prophylactic. Effects, if any, of gonadal extracts should be noted only during pre-pubescence and pubescence. Classification may be made of typal or proportionate and non-typal or disproportionate giants. Ten cases of overgrowth were noted in a series of 2000 endocrine cases. Eight of these potential giants were treated with gonadal extract in an effort to check growth. All were benefited. A case of unrestrained overgrowth is reported, together with four cases treated with gonadal extracts successfully. The last case was that of a male treated

with ovarian extract. The effect of gonadal extracts in gigantism must be evaluated by further experimental work, but this series indicates a probable antagonistic influence during adolescence.

REFERENCES

1. Bassoe, P.: Endocrine growth disturbance, acromegaly, gigantism, dwarfism, M. Clin. North America, **5**: 85. 1921.
2. Lisser, H.: Blumer's Bedside Diagnosis, Vol. III, p. 197. Saunders, Phila., 1928.
3. Hutchinson, Woods: The pituitary gland as a factor in acromegaly and gigantism. N. Y. Med. J. **72**: 89; 133. 1900.
4. Englebach, W. and J. L. Tierney: Disorders of the pituitary gland. Tice, Pract. of Med., Vol. VIII, 618. 1923.
5. Sutton, L. P.: Abnormal growth in a girl; report of case. Arch. Pediat. **44**: 109. 1927.
6. Lisser, H.: Personal communication.
7. Rowe, A. W.: Personal communication.
8. Teel, H. M. and H. Cushing: Studies in the physiological properties of the growth-promoting extracts of the anterior hypophysis. Endocrinology, **14**: 157. 1930.
9. Evans, H. M.: Science (Supplement), **75**: 10. 1932.
10. Butenandt, A.: Science (Supplement), **75**: 9. 1932.
11. Thayer, S. A., L. Levin and E. A. Doisy: Theelin; some physical and chemical properties. Biol. Chem. **91**: 199. 1931.

STUDIES IN THE EXPERIMENTAL PRODUCTION OF SIMPLE GOITRE*

BRUCE WEBSTER

From the Department of Medicine, School of Medicine,
Tulane University of Louisiana
NEW ORLEANS

Marine in 1921 began an address on simple goitre by saying—"The ultimate cause of simple goitre is totally unknown. The immediate cause is a lack of iodine." (1) He pointed out at the same time that is is essential to remember that this lack of iodine may be relative as well as absolute. It is with this "ultimate cause" which induces a relative iodine insufficiency that the studies which we are about to report have been concerned.

During the winter of 1928, in the course of some studies in experimental syphilis, at the Johns Hopkins Medical School, it became apparent that the average weight of the thyroid glands of the rabbits used in these experiments, as determined at autopsy, was steadily increasing. Browne, Pearce and Van Allen (2) had recently published statistics which fixed the average weight of the thyroid gland of the normal rabbit at 200 mgm. Marine (3) has since stated that he considers the normal weight of the thyroid gland of the rabbit to be between 75 mgm. and 150 mgm. A survey of our records for the years 1927 and 1928 showed the average thyroid weight of 500 control rabbits to be 2.9 grams or over ten times that of Browne, Pearce and Van Allen. Further analyses showed that the average weight for the animals in 1928 was considerably greater than that of the previous year. Accordingly, an attempt was made to discover the reason for this apparently localized epidemic of goitre. The fact was first established that all rabbits were without goitre on entering the laboratory. It was then shown that the degree of thyroid enlargement was directly proportional to the duration of time during which the animals were kept in the laboratory. Practically 100 per cent of the rabbits which remained in the laboratory for 40 days or more developed thyroid glands which were above the normal weight range. Glands weighing as much as 43 grams were encountered. It was apparent that we were dealing with a powerful goitrogenic agent.

Clinically, in most instances, the necks of these animals bulged, producing a dew-lapped appearance (Figure 1). Stridor was sometimes present. Pathologically, these goitres were typical *struma parenchymatosa diffusa*. The glands were soft and very vascular. Microscopically, they

*Read before the Association for the Study of Internal Secretions, New Orleans, May 10, 1932. Much of the material presented in the following address is a summary of previously published papers and represents the work of a number of individuals, especially Dr. Alan Chesney, Dr. David Marine, Dr. Emil Baumann and Miss Anna Cipra.

Figure 1. Photograph of rabbit No. 882 showing large simple goitre.

showed a simple diffuse hyperplasia. Infoldings rarely occurred (Figure 2). It has since been pointed out by Marine that this lack of infolding is due to the small size of the follicles of the rabbit thyroid. Except for a slight increase in heart, body weight ratio, the animals were otherwise normal.

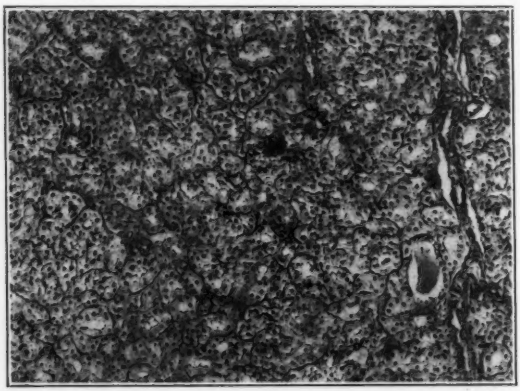


Figure 2. Photomicrograph of thyroid gland of rabbit shown in Figure 1, showing extreme hyperplasia (x 100).

The rabbits in which this outbreak of goitre occurred were of all common breeds and had been obtained from various dealers in Maryland and Pennsylvania. They were kept in individual cages in the animal rooms of the Johns Hopkins Hospital. Their diet consisted of a daily ration of 250 grams of cabbage and a weekly ration of 20 grams of hay and 50 grams

of oats. The cabbage was procured from various regions of Eastern United States, ranging between Florida and New York State with the season.

In an effort to determine the etiological factor in the epidemic of goitre with which we were dealing, a series of controlled experiments was devised. As these experiments progressed, it soon became apparent that the cabbage in the diet of these rabbits was the factor which produced the goitre. Animals maintaind on hay and oats did not develop thyroid enlargement. Marine confirmed this finding (4).

The question then arose as to whether or not the cabbage diet was the sole etiological factor in the production of the goitre in our rabbit colony. Because of the extensive work of McCarrison (5) on the role of the food contamination in the production of simple goitre, a series of experiments was carried out in which the animals were kept under conditions designed to prevent, as far as possible, fecal and urinary contamination of the food. Rabbits maintained under such conditions for one year developed the same degree of thyroid enlargement as did the control group kept under standard conditions. It was also demonstrated that the addition of water, either tap or distilled, to the diet, exerted no appreciable influence on the goitrogenic agent. The addition, however, of 7.5 mgm. of iodine per week to this diet completely protected a group of rabbits for a period of 420 days, whereas all of the control group developed goitres.

Thus far we had established the fact that the feeding of cabbage to rabbits in quantities equivalent to 60 calories per kilogram per day would produce hyperplasia of the thyroid and that the degree of hyperplasia was to some extent proportional to the duration of feeding. Further, we had shown that the addition of iodine to this diet would entirely prevent it. In this latter respect, the condition with which we were dealing resembled all other forms of simple goitre.

As the investigation continued, the observation was made that goitre was more easily produced during the winter months (October to March) than during the summer (April to September). Further, large goitres which had developed during the winter months tended to decrease in size during the summer. An analysis of the thyroid gland weights for the years 1927 to 1929, inclusive, confirmed this observation that the goitrogenic influence was apparently more active during the winter months. During the winter of 1929 to 1930 an attempt was made to secure definite information regarding this seasonal variation. Cabbage was obtained from a constant source in northern New York State. This was harvested at weekly intervals and its goitrogenic power was tested by rabbit feeding. Here it was observed that early in November some abrupt change occurred which rendered the cabbage goitre-producing. It was felt that this change was in some way concerned with the maturation of the plant. This cabbage could be kept in cold storage and was capable of producing goitre at any season of the year. These experiments were repeated with the same results during the winters of 1931 and 1932.

It was further evident that lots of cabbage from the same geographic source varied in their goitre-producing power from year to year, apart from the seasonal variations described above. Attempts were made to correlate this yearly variation with meteorological conditions. It was thought that some relationship existed between the total amount of sunlight during the growing season and the goitre-producing power of cabbage.

The important role which iodine has always played in the etiology of simple goitre constantly brought up the question, could all this not be due simply to variations in the iodine content of the cabbage? One had only to work with the problem a relatively short time before it became apparent that we were dealing with a goitrogenic agent much more powerful than any iodine-deficient diet. Rabbits could be injected with as much as 10 mgm. of iodine at the beginning of an experiment and yet show, after four weeks of cabbage feeding, thyroid glands three times normal size. Further, wide variation in the iodine content of the cabbage could occur without altering the goitre-producing power. Cabbage with a relatively high iodine content sometimes had a high goitrogenic activity and vice versa. Determinations of the iodine content of samples of New York State and South Carolina cabbage were made. The dried whole New York cabbage was found to contain 98 parts of iodine per billion. The iodine content of dried cabbage grown near Charleston, S. C., was 109 parts per billion.† The goitrogenic activity of these two lots, with approximately the same iodine content, was found to differ widely. The Charleston sample had little or no goitrogenic activity, while the New York State sample, when tested under the same conditions, was moderately goitrogenic. Experiments of this nature demonstrated very early in the work that we were dealing with some agent which had the power to deplete the normal iodine store of the animal organism and thus create a relative iodine insufficiency, rather than an absolute one on the basis of dietary intake.

McCarrison working in India confirmed our findings that cabbage fed to rabbits or rats would produce goitre (6). Further, he established independently the fact that there was a seasonal variation during what corresponded to the Indian equivalent of our autumn. He also demonstrated that the goitrogenic activity of cabbage bore no relationship to its iodine content.

The question arose as to whether or not plants other than cabbage were capable of producing goitre. Although an extensive survey along this line has not been made, it was found that other members of the Brassica group of vegetables (Brussels sprouts and cauliflower) were goitrogenic, while some of the other groups were not goitre-producing.

An attempt was then made to determine the mechanism whereby these plants were capable of causing thyroid hyperplasia. Was it due to the presence or absence of some substance in the vegetable? Was the goitrogenic factor a positive one or a deficiency phenomenon? Repeated experi-

†We are indebted to Dr. Roe E. Remington of the South Carolina Food Research Laboratory, Charleston, for making the iodine determinations.

ments had already demonstrated that when an active goitre-producing cabbage was dried in air or in vacuo, it lost completely its goitrogenic power. Similarly, various extractives, such as ether and acetone, caused the cabbage to lose its power of producing goitre. These observations tended to suggest that we were dealing with a positive and not a deficiency factor.

A few of the properties which throw some light on the nature of this substance have been demonstrated. Steaming the cabbage for 30 minutes increased its goitrogenic activity. When this steamed cabbage was pressed, the residue or cake contained all of the goitre-producing material, while the juice contained none. This substance was not readily soluble in water, either at room temperature or 100°C. Mild acid hydrolysis did not destroy it. Alkaline hydrolysis destroyed it to a slight extent.

The goitre-producing power of these various extracts was tested by feeding them in caloric equivalent quantities to normal rabbits which had been injected subcutaneously with 10 mgm. of potassium iodide one week prior to the beginning of the experiment. By this injection of potassium iodide an attempt was made to standardize the animals and to insure a well involuted thyroid with which to begin. If the thyroid was not from two to three times normal size at the end of four weeks of such feeding, the cabbage or extract being tested was considered inactive.

At this stage of the experiment, it was felt that, although very little was known about the nature of this substance which was apparently widely spread in plants, its presence had been established and perhaps a means of readily producing goitre in a common laboratory animal had been provided. This in itself, we hoped, might enable some light to be thrown on the still obscure question of the etiology of simple goitre.

This method for the production of simple goitre has been made use of to study several aspects of the disease during the past three years. As far as can be determined, the simple goitres obtained in this manner present the same pathological and physiological reactions as all other forms of simple goitre in man or animals. The respiratory metabolism of the goitrous rabbits is 18 to 20 per cent below the established normal for control animals. Early in the course of the experiments, it was considered of interest to know the effect of the administration of iodine on the respiratory metabolism of these animals. Accordingly 7.5 mgm. of potassium iodine was given daily to a group of animals with large goitres and the respiratory metabolism studied. To our surprise, the heat production rose rapidly to two or three times the normal level, the body weight fell and the animals died within 48 to 72 hours after the administration of iodine was begun. The experiment was then repeated using animals with smaller goitres and reducing the quantity of potassium iodide administered. After a single dose of 5 mgm. of potassium iodide, we obtained a gradual increase in heat production to approximately twice the normal level. This persisted for from 5 to 10 days and then gradually returned to a level slightly above

the previous myxedematous one. The administration of a second 5 mgm. brought about a much less severe reaction. This experiment was repeated many times using varying amounts of iodine. Briefly, the results indicated that the quantity of thyroid hormone which these hyperplastic glands were capable of elaborating, as indicated by the increase in heat production, was directly proportional, within certain limits, to the amount of iodine which was available. This relationship held true until involution was nearly complete. The time periods over which these metabolic changes occurred confirmed Marine's (7) observations, made on tadpoles several years ago, that, although the storage of iodine in a hyperplastic thyroid gland might occur very quickly, its elaboration into thyroxine did not take place for many hours or days.

Apparently these hyperplastic glands were potentially capable of manufacturing more than the normal requirement of thyroxine, if the necessary iodine was available. It would seem possible that this reaction which had been brought about here was essentially the same thing as the much discussed "iodine Basedow's" which is described from time to time in the medical literature. If an individual with a large simple goitre were suddenly given large quantities of iodine, it does not seem unlikely that a similar reaction would occur.

The development of large goitres in these rabbits provided an ideal means of studying thyroid involution. By injecting varying amounts of iodine and taking frequent biopsies from the thyroid glands, it was possible to observe involution under controlled conditions. The degree of involution, as would be expected, depended on the amount of available iodine together with the time period over which it was allowed to act. By carrying these two factors one could obtain all stages from complete hyperplasia to a colloid goitre, or complete involution, at different times in the same animal.

During the course of these studies an opportunity was afforded to observe the microscopic changes which occurred in the hyperplastic gland in response to iodine. In the thyroid glands of the animals exhibiting moderate or extreme degree of hyperplasia, the acini were composed almost entirely of cells of the so-called "chief" type of Langendorff (8). These cells had large vesicular nuclei and a reticular protoplasm. Following the injection of even minute quantities of iodine, there was a sudden transition from this type of acinar cell to those of the "colloid" type. That is, they became acid staining with small pyknotic central nuclei and a clear transparent protoplasm. There has been in the past considerable conjecture as to the significance of these two cell types in the thyroid acinus and their functional status. Langendorff (8), Bensley (9) and Uhlenhuth (10) have regarded them as two distinct cell types which had different secretory functions. From the observations which we have been able to make on the occurrence of these two cell types and the correlation of these observations with the functional activity of the thyroid gland as a whole, as determined

by heat production, it would seem that they probably are the same cell type in different stages of functional activity.

Within the past few months two slight advances have been made in our efforts to determine the nature of this goitre-producing substance. Because of the apparent influence of the amount of sunlight, during the growing season of the cabbage, on the quantity of goitre-producing substance in this cabbage, it was felt that perhaps sunlight might bring about a photosynthesis of this substance in the plant. Accordingly, the simplest possible experiment which might give us some information along this line was made. Finely divided cabbage, which was known to be goitrogenic, was irradiated for 20 minutes at a distance of 1 metre with a carbon arc which produced rays with a maximum intensity at 3800 Angstrom units. This cabbage was then tested for goitre-producing power by feeding to rabbits under the standard conditions previously described. The experiment was controlled by feeding unirradiated cabbage from the same lot to a similar group of rabbits. It was found that the irradiated cabbage had twice the goitreogenic power of the unirradiated. This experiment was repeated a second time with the same result. It would appear that sunlight does play a role in the production of this goitre-producing substance, and the evidence at hand would suggest that this reaction must be in the nature of a photosynthesis. Further investigation is in progress along this line.

The other recent development in this work has been reported by Dr. Marine and his associates (11). For some time it has been felt that the goitre-producing substance in plants might be a glucoside. It is well known that the glucoside content of many plants is susceptible to seasonal variation and what information was available concerning the properties of this substance was compatible with its being a glucoside. Numerous unsuccessful attempts were made to isolate the cabbage glucoside in quantities sufficient for our purpose. Hoffman (12) had previously shown that cyanides were components of the glucosides of the Brassica group of vegetables. On the supposition that these cyanides might be the substances which increased the needs of the organism for the thyroid hormone by partially blocking tissue oxidation, Marine and his associates injected subcutaneously into young rabbits, a number of cyanide compounds. All of these produced thyroid hyperplasia. Marine has suggested that this hyperplasia was the result of a compensatory attempt to overcome the depression of oxygen consumption which was caused by the cyanides, and that this mechanism may be an essential factor in the causation of simple goitre.

CONCLUSION

In conclusion, it would appear that there exists, in certain plants and vegetables, a goitre producing substance which is subject to considerable seasonal and geographic variation and which produces its effect by a depression of tissue oxidation. The latest evidence suggests that this sub-

stance is a cyanide. When the depression of tissue oxidation occurs, it would seem that an effort is made on the part of the thyroid to compensate for this by an over production of that activator of oxidation, thyroxine. This, in turn, probably brings about a relative iodine insufficiency and a consequent hyperplasia of the thyroid gland. Such an explanation is compatible with our present knowledge of simple goitre. Whether or not the geographic variation in the content of this substance in plant and vegetable life bears any relationship to the geographic distribution of simple goitre, remains to be investigated.

A certain amount of the simple goitre which exists today may be due to an absolute iodine insufficiency. However, modern transportation methods have largely abolished the localized dietary sources which existed in the Swiss cantons of a century ago. It is hard to believe that all of the individuals who now have simple goitre, have been subject to an absolute insufficiency of iodine in their diets. It would seem, rather, that we must turn our attention to the question of the circumstances which induce a relative insufficiency in the individual. Whether this be intrinsic in the patient, as in the simple goitre of pregnancy, or due to the ingestion of some substance which disturbs the normal mechanism of biological oxidation, as in the goitre of rabbits produced by feeding cabbage, the result is the same. There is a compensatory demand for more thyroxine, which is met by the thyroid. If this demand is too great or too prolonged, simple goitre results.

It would seem, then, that future investigation into the causes of simple goitre must be along the lines of attempts to discover the inherent disturbance in the animal organism which is capable of producing a relative iodine insufficiency. Depression of tissue oxidation, with its consequent demand for an increased production of thyroxine, is one of the most likely causes of this relative insufficiency. With the rapid advances which are taking place in the field of biological oxidation, it is not unlikely that a better understanding of the etiology of simple goitre may soon be available and that the "ultimate cause" of this condition will be understood.

SUMMARY

A series of experiments is reported in which it has been shown that simple goitre can be produced in rabbits by the feeding of cabbage and other plants. There is contained in these plants a substance which is capable of depressing tissue oxidation in the body and causing, as a result, an increased demand for thyroxine. This brings about a relative iodine insufficiency, which, in turn, produces hyperplasia of the thyroid gland. There is considerable seasonal and geographic variation in the amount of this substance contained in various plants. Irradiation with ultraviolet

light increases the goitrogenic activity of the plants. Simple goiters produced in this manner resemble essentially all other simple goitres in man and animals in their physiological and pathological reactions.

REFERENCES

1. Marine, D.: J. A. M. A., **77**: 1068. 1921.
2. Brown, W. H., L. Pearce, and C. M. Van Allen: J. Exper. Med. **62**: 69. 1925.
3. Marine, D.: Personal Communication.
4. Marine, D., E. J. Baumann and A. Cipra: Proc. Soc. Exper. Biol. & Med. **26**: 822. 1929.
5. McCarrison, R.: The Simple Goitres, Wm. Wood & Co., N. Y., 1928.
6. McCarrison, R.: Indian J. M. Research, **18**: 903. 1931.
7. Marine, D. and J. M. Rogoff: Pharmacol. & Exper. Therap. **9**: 1. 1916.
8. Langendorff, O.: Arch. f. Anat. u. Physiol. **219**: (Suppl.) 1889.
9. Bensley, R. R.: Am. J. Anat. **19**: 37. 1916.
10. Uhlenhuth, E.: Anat. Record, **27**: 223. 1924.
11. Marine, D., E. J. Baumann, A. W. Spence and A. Cipra: Proc. Soc. Exper. Biol. & Med. **29**: 772. 1932.
12. Hoffman, A. W.: Ber. d. chem. Ges. **7**: 518. 1874.

SPONTANEOUS ACTIVITY IN MALE RATS IN RELATION TO TESTIS HORMONE*

RICHARD E. HELLER
Hull Zoological Laboratory, University of Chicago
CHICAGO

I. THE PROBLEM

The preparation by McGee (6) of extracts of bull testes that stimulated growth of the comb of castrated cocks and the subsequent advances in the purification of these extracts by Gallagher and Koch (1, 2) are now well known. Similarly, through the publications of Moore and his associates (7, 8, 9), it has been demonstrated that these extracts prevent the onset of castration changes in the mammal, or repair them if administered subsequent to castration damage [Vatno (14), Heller (4)]. Several mammalian test methods have been utilized, all of which have dealt with the accessory organs of reproduction. Since it is necessary to know that these preparations are effective in preventing all changes known to follow castration before arriving at the conclusion that they contain the complete hormone, I have made a study of the spontaneous activity in the rat in relation to its hormone state to learn whether voluntary activity can be successfully used as a hormone indicator.

The voluntary activity of male rats, registered by recording revolving cages, has been determined by Wang (13) and Hoskins (5) to be materially reduced by removal of the testes. Reductions of 50 per cent or more in the activity of groups of castrates in comparison with controls have been reported and one might assume that the lowered response is due to a reduction in the hormone content of the castrated group. Gans (3), however, states that castration as early as ten days after birth fails to cause a difference in voluntary activity in castrates and controls up to one hundred days of age. Hoskins was unable to increase the spontaneous activity of castrated rats by injection of macerated testes but Richter and Wislocki (11) report greater activity in castrated males bearing testis grafts than in non-transplanted or unsuccessfully transplanted ones.

In the following pages the results of a series of studies will be reported briefly in which an attempt was made to determine, *first*, whether the spontaneous activity of individual males, in contrast to groups of males, offered a dependable means of detecting the presence of testis hormone and, *second*, to determine whether the administration of potent testis extracts could successfully prevent the loss of activity after castration.

The white rat served as experimental material and the recording apparatus, manufactured by E. A. Kaestner, Baltimore, Md., consisted of four

*This investigation has been aided by a grant from the Committee on Research in problems of sex of the National Research Council; grant administered by Professor F. R. Lillie.

tiers of four cyclometer cages. Observations have been made upon approximately 90 males usually in groups of 16. They have been followed during all seasons of the year and under different lighting and food conditions. Five series are reported here; the first three (A, B, and C) were allowed to feed on a balanced diet during the whole day, while series D and E were fed only one hour per day, during which period the cages were cleaned, readings taken, and injections made. The room containing the cages was kept quiet and at approximately constant temperature.

II. ACTIVITY OF NORMAL MALES

Each group of 16 males was composed of healthy animals of similar age selected from the stock colony; the different groups varied somewhat in age (from four months to a year) at the beginning of an experiment. Cage adaptation was usually attained by about the twentieth day and although the daily running performance is known for each animal from the beginning, the cardinal points of this paper will be concerned with periods following establishment of their typical activity level.

Among each series of males selected for an experiment there was a wide range of individual performance and the animals could be rated quite early into low, intermediate and high activity groups. In table 1 the total

TABLE I

VARIATIONS IN THE ACTIVITY OF NORMAL WHITE RATS FOR THIRTY DAYS AFTER CAGE ADAPTATION

Rat Number	Date at Beginning	Total Number Revolutions Per Period	Rat Number	Date at Beginning	Total Number Revolutions Per Period
3E	2/15	18,570	3A	5/ 6	16,528
4E	2/15	20,306	4A	5/ 6	22,222
6E	2/15	2,944	9A	5/ 6	93,508
4C	3/ 3	44,674	10A	5/ 6	6,632
5C	3/ 3	5,429	11A	5/ 6	95,160
6C	3/ 3	500	13A	5/ 6	131,197
7C	3/ 3	7,834	14A	5/ 6	118,641
9C	3/ 3	75,773	15A	5/ 6	182,250
10C	3/ 3	36,036	16A	5/ 6	316,833
11C	3/ 3	12,632	3B	11/ 1	2,831
12C	3/ 3	16,725	16B	11/ 1	7,989
15C	3/ 3	5,430	4D	11/10	58,986
16C	3/ 3	41,853	8D	11/10	1,609

number of revolutions of the cage for a period of 30 days subsequent to cage adaptation is given for 26 animals selected to represent all periods of the year. Thus when animals No. 4C and 6C are compared for the period of 30 days following March 3, the high activity of 44,674 revolutions (a daily average for the period of 1489 revolutions) is in striking contrast to the low of 500 (a daily average of 16 turns). Again, animals 16A and 10A giving the performance for 30 days following May 6 represent the high runners (a total of 316,833 and a daily average run of 10,561) and low (6,632 total and a daily average of 221). The daily activity per individual was seen to vary tremendously from day to day; changes in running levels for each 24 hours were observed which differed from the preceding level by as much as 10,000 revolutions.

It was at once suspected that the low runners of a group, though apparently entirely healthy, normal animals, might represent individuals with a low testis hormone secretion. Examination of the accessory reproductive organs by the techniques employed in this laboratory for hormone detection, however, revealed the fact that these low running males were actively secreting testis hormone. The prostate glands and seminal vesicles were large and distended with secretion. The prostate glands exhibited a normal secretory epithelium (with prominent light spots), and the seminal vesicle epithelium contained numerous large secretion granules. Cowper's glands were similarly normal in appearance. These criteria are dependable indicators of the presence of testis hormone in high concentration; diminution or loss of hormone secretion is quickly registered by these objective indicators.

It becomes evident from such observations that spontaneous activity of the animal is by no means proportionate to testis hormone secretion.

III. INJECTION OF TESTIS HORMONE AND GONADAL-STIMULATING HORMONE INTO NORMAL ANIMALS

(A). Bull testis extract kindly supplied by Koch and Gallagher of the Department of Physiological Chemistry and previously assayed in bird units was injected into normal animals selected from the running range of animals of different groups in order to determine whether the administration of additional hormone to the normal animal affected its running rate. Subsequent to cage adaptation, animals of the low, intermediate or high activity were given subcutaneous injections of testis hormone in different concentrations, and a given period of injection for each animal was compared with a period of similar length immediately preceding injection, and in some cases immediately succeeding the period of injection. Table 2

TABLE II

THE EFFECT OF INJECTIONS OF TESTIS HORMONE, HEBIN, AND SALT SOLUTION ON THE ACTIVITY OF NORMAL ANIMALS

Animal No.	Dose	Duration of Each Period	Total Revolutions for Periods of Equal Length			
			Before Injection	During Injection	Change in Activity	After Injection
1A	1 B. U.	10 days	7,545	16,000	+112%	17,646
6A	1 B. U.	10 days	38,649	35,789	— 7%	43,550
12A	1 B. U.	10 days	114,345	110,914	— 3%	99,541
5B	2.5 B. U.	20 days	4	14		
13B	2.5 B. U.	25 days	3,491	5,405	+ 54%	
1B	2.5 B. U.	25 days	3,930	3,693	— 6%	
2B	2.5 B. U.	25 days	41	10		
14D	7 B. U.	20 days	21,362	35,647	+ 66%	
15D	7 B. U.	20 days	30,928	35,997	+ 16%	
1D	1 cc. hebin	15 days	63,011	48,271	— 24%	54,903
2D	1 cc. hebin	15 days	63,603	19,794	— 69%	19,925
5D	1 cc. hebin	15 days	54,346	17,024	— 69%	17,615
11D	1.5 cc. hebin	25 days	15,843	9,810	— 38%	
12D	1.5 cc. hebin	25 days	8,379	16,344	+ 49%	
3D	1 cc. NaCl	15 days	3,251	2,417	— 26%	
7D	1 cc. NaCl	15 days	17,609	21,466	+ 22%	

B. U.—Bird units of male hormone.

presents observations made upon nine animals injected with different dosages of testis hormone. It is readily observed that the response of the animal is in no way proportional to the amount of hormone introduced. Animals 1A and 6A received each one bird unit of testis hormone daily for 10 days. The total running performance during the injection period in comparison with the 10-day period preceding injection was a gain for 1A of 112 per cent and for 6A a loss of 7 per cent. Animals 13B and 1B receiving daily injections during a period of 25 days of two and one-half bird units showed respectively a gain of 54 per cent and a loss of 6 per cent. Animals 14D and 15D, receiving a daily injection of seven bird units for a 20-day period, gained 66 per cent and 16 per cent.

It is clearly demonstrated that the injection of testis hormone into normal males does not lead to an increase in total activity proportional to the amount of hormone introduced, nor does the addition of hormone result in any consistent effect upon the total activity of the animal.

(B). The concentration of testis hormone in the body of an animal can be increased, perhaps more effectively than by injecting the hormone directly, if excessive hormone secretion by the testis is stimulated by the administration of gonadal stimulants. Wallen-Lawrence and VanDyke (12) have prepared "hebin" from human pregnancy urine, an extract that has a pronounced effect upon the activity of the gonads. Moore and Price (10) have reported the effects of this extract upon the reproductive system of the male rat and I have tested its action upon their voluntary activity by means of hypodermic injection in five cage-adapted animals. The concentration employed was an effective gonadal stimulant as shown by the enlarged, secretion-distended seminal vesicles. The substance in the absence of the testes is ineffective in preventing castration changes, hence it operates by stimulating the testis to excessive endocrine activity which is indicated in turn by the state of the reproductive accessories.

Despite the overproduction of testis hormone, table 2 shows that four of the five treated males exhibited a decline in their running rate during the injection period. Periods of 15 to 25 days, during which injections were given, when compared with a similar period immediately preceding injection, showed a reduction in total running of from 24 to 69 per cent. The fifth animal showed an increase of 50 per cent. Of two animals injected with an amount of normal salt solution similar to the hebin injections, one showed a gain in running for the period of injection of 22 per cent and the second one a loss of 26 per cent. Three hebin-injected animals exhibiting a loss during the period of injection failed to return to the pre-injection level in a similar period of time after injections had been discontinued.

It is strikingly evident from these results that the total spontaneous activity of the animal cannot serve as a criterion of the level of testis hormone in the body. Excessive secretion by the intact testis was accompanied by decidedly lower running rates in four of five animals.

IV. THE EFFECTS OF CASTRATION; AND OF TESTIS REMOVAL FOLLOWED BY INJECTIONS OF HORMONE

(A). Fourteen animals showing different grades of activity were castrated. Some of these registered a loss in activity but others registered decided gains (Table 4, 9D and 16D). This rise might start the week after castration and persist throughout the experiment. The record of 10 animals is given in table 3. These rats show a reduction of from 12 to 74

TABLE III
THE EFFECT OF CASTRATION ON SPONTANEOUS ACTIVITY

Rat Number	Total Number Revolutions Per 40 Days Before Castration	Total Number Revolutions Per 40 Days After Castration	Percent Drop in Activity
7E	89,172	71,281	21
8E	14,428	5,893	59
9E	54,828	42,679	12
10E	57,017	22,496	61
11E	83,518	65,517	22
12E	7,774	4,145	47
13E	37,000	14,757	60
14E	12,940	10,861	16
15E	82,466	22,264	74
16E	143,546	128,251	13

per cent for the period after castration. The daily activity of some of this group was so variable that at times the running level would reach the pre-castration range or even exceed it for short periods and then drop down to the lower level again.

It is not the purpose of this report to question the results of others who show that for group averages a reduction in total activity occurs after castration. Attention has rather been directed to the individual than to the group to determine the advantages of such a technique for the study of the effect of testis hormone on the animal. The results obtained do not recommend the activity of an animal as registered by cyclometer cages as a means of determining an effect of the testis hormone.

(B). Four animals were castrated and then given injections of testis hormone, the results of which are given in table 4. The record includes

TABLE IV
THE EFFECT OF CASTRATION AND INJECTION OF SEVEN BIRD UNITS OF TESTIS HORMONE ON ACTIVITY

Rat Number	Average Activity Per Day				
	For 25 Days Before Castration, After Cage Adaptation	For a Castration Period of 25 Days		During an Injection Period of 15 Days	
			Change in Activity		Change in Activity
9D	3,406	5,623	+ 65%	8,406	+ 49%
10D	2,916	1,826	— 38%	525	— 72%
13D	3,907	2,640	— 33%	4,296	+ 62%
16D	2,192	4,651	+112%	238	— 95%

the performance of these animals during 25 days preceding castration, for a similar period following castration, and for a further period of 15 days during which each animal received daily injections of seven bird units of testis hormone. This amount of hormone prevents the appearance of all morphological indications of castration in the accessory reproductive organs, or repairs a castrate condition to the normal state as was apparent on histological examination of the accessory glands of these four rats.

The total lack of dependence of the activity to register the hormone state of the body is revealed in the table but attention should again be directed to animals 9D and 16D. Castration in both was followed by an increase in total activity for the period, rather than by a decrease; the amount was 65 and 112 per cent increase. The injection of strong doses of testis hormone daily for 15 days was accompanied in the former by an increase of activity of 49 per cent over that shown during the period of castration alone, whereas in the case of the latter animal a loss of 95 per cent of its activity was registered.

DISCUSSION

The observations presented above would appear to demonstrate conclusively that the total voluntary activity of a male rat as registered by recording cyclometer cages is not an adequate technique by means of which to study the effects of testis hormone upon the organism. While the general contention of others that the average activity of groups of castrated animals is lower than groups of normal animals, it is not of particular consideration here. The fact remains that total activity fails to offer any suggestion in regard to the hormone state of the individual. Thus normal healthy animals may show but very little running activity while the testis hormone concentration in the body is maximal when judged by the morphological state of the accessory reproductive organs.

That voluntary activity is inadequate to indicate the hormone state of the individual is shown by the fact that (1) untreated normal males possessing a high concentration of testis hormone as shown by the condition of the accessory glands of reproduction may vary in total running performance for a period of 30 days by as much as 4700 per cent; (2) injections of testis hormone into normal males is not followed by any consistent trend in activity; (3) increasing the endocrine activity of the testis many-fold by introducing gonadal stimulants fails to modify the total activity in any consistent manner; (4) castration in the individual, in contrast to group averages, fails to give consistent modifications of the running performance; (5) castration followed by injection of heavy doses of testis hormone is not followed by consistent trends in activity.

SUMMARY

The relationship existing between spontaneous activity and testis hormone in rats was studied from several angles in an attempt to ascertain

whether activity could be used as a criterion of the endocrine state of the animal. Normal males, with established activity levels, were injected with heavy doses of testis hormone, and other normals with the sex-activating principle of the pituitary gland, which stimulates gonad hormone production. The results were not constant; some animals showed a drop in activity and others a rise. Another group was castrated following which a depression in activity was noted in most of them; however, in two cases there was an increase. Injections of testis hormone in castrates did not produce any definite changes in running level. Considerable variability was also observed in normal controls.

From this series of experiments it is seen that voluntary activity of white rats does not give a constant response to alterations in testis hormone level, and therefore is of little value as an indication of the amount of hormone produced by the testes or of the potency of testis extracts. It appears that this hormone is at least not the sole factor involved in spontaneous activity.

I am indebted to Dr. Carl R. Moore for suggesting and guiding the experimental procedures; to Professor F. C. Koch and Dr. T. F. Gallagher for the preparations of testis hormone employed in the injections; and to Professor H. B. Van Dyke and Zonja Wallen-Lawrence for active preparations of the gonad stimulating substance prepared from pregnancy urine.

REFERENCES

1. Gallagher, T. F. and F. C. Koch: The testicular hormone. J. Biol. Chem. **84**: 495. 1929.
2. Gallagher, T. F. and F. C. Koch: The quantitative assay for the testicular hormone by the comb growth reaction. J. Pharmacol. & Exper. Therap. **40**: 327. 1930.
3. Gans, H. M.: Studies on vigor. XIII. Effect of early castration on the voluntary activity of male albino rats. Endocrinology, **11**: 141. 1927.
4. Heller, R. E.: Cowper's gland and its reaction to castration and to different sex-hormone conditions. Am. J. Anat. **50**: 73. 1932.
5. Hoskins, R. G.: Studies on vigor IV. The effects of testicle grafts on spontaneous activity. Endocrinology, **9**: 277. 1925.
6. McGee, L. C.: The effect of the injection of a lipoid fraction of bull testicle in capons. Proc. Inst. Med. (Chicago), **6**: 242. 1927.
7. Moore, C. R. and T. F. Gallagher: Seminal vesicle and prostate function as a testis hormone indicator; the electric ejaculation test. Am. J. Anat. **45**: 39. 1930.
8. Moore, C. R., Winefred Huges and T. F. Gallagher: Rat seminal vesicle cytology as a testis hormone indicator and the prevention of castration changes by testis extract injection. Am. J. Anat. **45**: 109. 1930.
9. Moore, C. R., Dorothy Price and T. F. Gallagher: Rat prostate cytology as a testis hormone indicator and the prevention of castration changes by testis extract injection. Am. J. Anat. **45**: 71. 1930.
10. Moore, C. R. and Dorothy Price: Some effects of fresh pituitary homo-implants and of the gonad-stimulating substance from human pregnancy urine on the reproductive tract of the male rat. Am. J. Physiol. **99**: 197. 1931.
11. Richter, C. P. and G. B. Wislocki: Activity studies on castrated male and female rats with testicular grafts in correlation with histological studies of the grafts. Am. J. Physiol. **86**: 651. 1928.
12. Wallen-Lawrence, Zonja, and H. B. Van Dyke: The gonad-stimulating substances of the anterior lobe of the pituitary body and of pregnancy-urine. J. Pharmacol. & Exper. Therap. **43**: 93. 1931.
13. Wang, G. H.: The relation between "spontaneous" activity and oestrous cycle in the white rat. Comp. Psychol. Monograph, **2**: 1. 1923.
14. Vatna, S.: Rat vas deferens cytology as a testis hormone indicator and the prevention of castration changes by testis extract injections. Biol. Bull. **58**: 322. 1930.

EVIDENCE ON THE CHIEF FUNCTION OF THE ADRENAL CORTEX*

S. W. BRITTON, B.S., M.D.
Physiological Laboratory, University of Virginia Medical School
UNIVERSITY, VIRGINIA

Studies have been carried out during the past eight years on the changes produced in animals by partial and by complete adrenalectomy. In the past two years the physiological effects of cortico-adrenal extract have been particularly noted. An extract of the adrenal cortex prepared by a modified Swingle-Pfiffner technique (8) has been chiefly used (2). The Swingle-Pfiffner method of extraction is slow—it takes two weeks to prepare a batch of extract; it is expensive—the cost of 100 cc. is about $30; it is nevertheless a sure method of preparing potent extracts of the cortical tissues. Again, however, large amounts of extract are necessary in order to produce results.

We have prepared to date over 130 batches of cortico-adrenal extract and invariably find that the material is potent. All the extracts contain adrenaline in the concentration of 1 part in 2 millions. We have therefore used adrenaline controls throughout our studies. Briefly, the following experimental results have been obtained.

Cortico-adrenal extract maintains completely adrenalectomized animals alive and in good health apparently indefinitely. It abolishes in a few hours the severe symptoms of adrenal insufficiency when these are allowed to develop (2).

Beside the general conditions which follow adrenalectomy—loss of weight, anorexia, weakness, convulsions—there are also found *decreases* in the neutrophiles in the blood and the total leucocyte counts (6), and in the blood sugar and liver and muscle glycogen (4); and *increases* in blood lymphocytes and erythrocytes and in blood concentration (6), in blood lactic acid and nonprotein nitrogen, and in serum calcium and phosphorus (4). All these evidences of a profoundly disorganized metabolism in adrenal insufficiency disappear under the influence of cortico-adrenal extract, and normal conditions are re-established.

The extract is definitely effective when given by mouth, although 3-5 times the usual intraperitoneal dosage is necessary (1). The severe prostration and convulsions of adrenal insufficiency may be alleviated and the animal restored within an hour after oral administration of the extract. Subcutaneous, intramuscular, intravenous and intracardial methods of injection have been used and found effective.

*Read by title before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 10, 1932.

The energy output of dogs running in a treadmill is increased 100 per cent or more above the normal following injection of the extract (7). The effect on the working capacity of animals extends over a period of about ten days.

Cortico-adrenal extract is markedly effective in producing precocious sexual maturity in white rats (5). The effect is most pronounced and appears first in the female animal.

It appears undoubted that the changes in carbohydrate metabolism in adrenal insufficiency are of outstanding significance. The changes in liver glycogen and in blood sugar after adrenalectomy are in themselves wholly sufficient to produce death of the animal. In pancreatectomized (diabetic) and also in hepatectomized animals the carbohydrate values are no more profoundly influenced than in adrenalectomized animals.

The general recovery of the animal after administration of cortico-adrenal extract is invariably associated with the restoration of the blood sugar and liver glycogen levels to normal; recovery would appear indeed to depend chiefly on the increased amounts of carbohydrates made available to the animal by the extract.

Extracts of the adrenal cortex definitely augment the blood sugar and liver and muscle glycogen values in normal animals (3).

The observations indicate that cortico-adrenal extract is a very important glycotaxic agent. It may possibly be considered to represent a very important "missing link" amongst hormones in view of this idea of its function.

In all probability there are two hormones contained in the present relatively crude extracts of the adrenal cortex which are employed. One may be considered a sex-stimulating agent, and the other an essential life-maintaining hormone. The sex-stimulating hormone is not essential.

The medulla of the adrenal glands, although admittedly of considerable importance in the ordinary activities of life, is not indispensable. The adrenal cortex, however, is vitally necessary to the organism.

By experiment and by deduction it is indicated that the chief function of the adrenal glands is the maintenance—in co-operation admittedly with other tissues—of normal carbohydrate inter-relationships in the organism.

REFERENCES

1. Britton, S. W., J. C. Flippin and H. Silvette: Am. J. Physiol. **99**: 44. 1931.
2. Britton, S. W. and H. Silvette: Am. J Physiol. **99**: 15. 1931.
3. Britton, S. W. and H. Silvette: Am. J. Physiol. **100**: 693. 1932.
4. Britton, S. W. and H. Silvette: Am. J. Physiol. **100**: 701. 1932.
5. Corey, E. L. and S. W. Britton: Am. J. Physiol. **99**: 33. 1931.
6. Corey, E. L. and S. W. Britton: Am. J. Physiol. In press.
7. Eagle, E. and S. W. Britton: Science. **75**: 221. 1932.
8. Swingle, W. W. and J. J. Pfiffner: Am. J. Physiol. **96**: 153. 1931.

EFFECT OF ADRENALINE CHLORIDE ON THE PROLIFERATIVE ACTIVITY OF THE CELLS OF THE ADRENAL MEDULLA

F. A. McJUNKIN, R. R. RALL AND P. L. SINGER
From the Department of Pathology, Loyola University School of Medicine
CHICAGO

Although we were primarily concerned in our investigation with the effect of epinephrine on the adrenal medulla various other anatomical changes attributed to its experimental administration have been considered. In spite of the profound toxicity and lethal effect of large doses of epinephrine the outstanding lesion is the "adrenaline myocarditis" of rabbits. Drummon (1) observed lesions in dogs after administration of 15 cc. of 1-1000 of epinephrine. The description of the pathological changes gives the impression that the lesions were of a mild degenerative type rather than destructive ones. Fleisher and Loeb (2), using the rabbit, produced extensive necrotic areas in the wall of the left ventricle by the intravenous injection of epinephrine and caffein. Samson (3) has lately studied the tissue change following continuous intravenous injections of epinephrine hydrochloride into the dog. He was of the opinion that changes seen in liver and kidney were due to a toxic action. They were reported as a fatty degeneration. No lesions were observed in the pancreas, aorta, heart, spleen, lungs, smooth and striated muscle. Ogata and Ogata (4), using toluidine blue as a histological test, observed that the depth of green in the adrenal medulla was proportional to the amount of epinephrine or pre-epinephrine substance present. They found only a trace of green after adrenaline administration. Samson confirmed these findings by demonstrating reduced amount of epinephrine content in the medullary cells in the dogs receiving intravenous epinephrine. In his histological studies he did not observe mitoses in the adrenal. Further confirmation of a diminished content of secretion within the gland following dosage with adrenaline was obtained by Cramer (5), who observed that the peripheral cells of the adrenal medulla lose their chromaffine staining after injections of epinephrine. He concluded from this that the adrenal gland has the power to control its functional activity in such a way as to prevent the gland from stimulating itself to complete exhaustion. One of the authors has participated in work on two of the endocrine organs which furnished morphological evidence of a very definite character to show that an endogenous secretion may have an inhibitory action on cell division. Insulin inhibited the normal proliferative activity of the pancreatic islets of infant rats (6). Parathyroid hormone arrested karyokinesis in the parathyroid glands (7). We have now extended our observations on these inhibitory effects to the adrenals.

METHODS

Wiesel's fixative was found best for our purpose which required good nuclear staining and at the same time a clear differentiation of the chromaffine cells. The two glands imbedded in paraffin were cut into 8-micron serial sections and were stained with hematoxylin and eosin. After this fixation, in spite of careful dehydration, the tissue was somewhat brittle and some sections in every set were undesirable for counting. We therefore calculated the number of mitoses on the basis of 100 sections that included medulla. The entire sets of slides were scanned with the aid of a mechanical stage, using a high-dry objective.

RESULTS

Suckling rats were chosen because preliminary experiments showed the proliferative activity of the adrenal medulla of these to be very great. In most instances litter mates were employed for the controls. From 1 to 3 rats were included in each experiment. In the normal control animals the karyokinetic rate of the medullary cells diminished as the age increased. At 11 days the average per 100 sections was well above 100, while at three weeks it was half that amount. At all ages (table 1) from the 8 to the

TABLE 1

No. of Experiment	No. of Rats in Experiment	Age in Days at First Injection	Age in Days When Killed	Time When Killed After Last Two Injections (Hours)	Doses of 1–10,000 Epinephrine (Intraperitoneal)	Mitoses per 100 Sections in Injected Animals	Mitoses per 100 Sections in the Control Animals
11A	3	1	11	3 and 27	0.01 cc. (2x) 0.1 cc. (5x)	37	
11B (control)	1		11				152
12A	3	18	25	24	0.2 cc. (5x)	2	
12B (control)	1		25				51
13A	2	6	20	1½ and 25½	0.1 cc. (10x)	2	
13B (control)	2		20				57
14A	1	8	11	24	0.3 cc. (2x)	60	
14B	1	9	13	3½ and 27½	0.3 cc. (3x)	31	
14C	1	10	14	8	0.3 cc. (3x)	6	
14D (control)	1		11				116
15A	3	6	8	9	0.45 cc. (3x)	70	
15B (control)	2		8				119

25 days the action of the epinephrine was pronounced. In the youngest animals (15A and 15B) it appears that the mechanism controlling growth is less readily influenced by the epinephrine. In the older animals (12A) the proliferative activity was brought almost to a standstill. The small dosage which we used appeared to be as effective as the larger. We were interested to know whether the effect on the adrenal medulla was a part

of a general arrest of development. An increase in weight of the injected animals indicated that it was not. To determine this more accurately we examined sections of kidney and liver of injected animals where we found abundant mitoses indicative of a normal growth. For example, where there was almost a complete arrest of mitotic activity in the adrenal medulla mitotic figures were very abundant in the epithelium of the kidney tubules.

Since the dosage was large a careful study of the various organs was made for toxic lesions. The liver, kidney, pancreas, spleen, stomach, intestine, lungs, aorta and heart were examined. Demonstrable histological changes were strikingly absent. In a few instances neutral fat was present in liver and kidneys. The presence of small amounts of fat in the parenchymal cells of these organs has a doubtful significance. It was in the myocardium only that definite destructive lesions were seen. The organ was so blocked that the sections included the walls of the left ventricle from apex to base. The lesions consisted of microscopic foci of necrosis in the ventricular wall. The necrotic foci were undergoing myomalacia and in 11A especially there were cellular foci in which the removal of necrotic fibers was already complete but the leukocytic reaction remained.

DISCUSSION

Previous investigations of a histological nature have given ample evidence that epinephrine injections decrease the content of the adrenal in this substance. From chemical data Tournade and Chabrol (8) concluded that injections of epinephine hydrochloride decreased the endogenous secretion. Such observations support the view that cell activity is a response to functional need and at the same time they throw light on the mechanism of the automatic control of function. There are obviously two main factors concerned in determining the amount of specific secretory substance produced by an organ. One of these is the rate of production by the individual cell and the other on which rests the potential ability of the gland to produce secretion is the number of gland cells. In the adrenal medulla the activity of the cell is inhibited by its own secretion. It may be assumed that a lessening of the amount of circulating epinephrine allows the activity of the chromaffine cell to be resumed. In our work with the adrenal and with the parathyroids and pancreatic islets we have been concerned with the mechanism determining the number of functional cells available in the gland rather than with the secretory activity of the individual cell. In the adrenal, an increased concentration of its own secretion in the plasma depresses its function and at the same time prevents the formation of new cells by mitotic division. Both factors concerned in producing the secretion are brought under inhibitory control. Resumption of functional activity following release of inhibition carries the implication that there are positive stimuli and that automatic regulation of cell activities is accomplished by the balance and unbalance of inhibitory and formative substances. Carrel (9) and his associates have

shown that cell proliferation in vitro may be brought about by growth stimuli in the form of polypeptids. In the living organism a determination of the activity of positive stimuli is more complex and no doubt less conclusive. One of us participating in a series of experiments has produced some evidence indicating that positive stimuli may affect the cells in their normal surroundings in the body (10, 11). Due to the rigid requirements necessary for the demonstration of the stimulant effects we were under the impression that the materials containing the stimuli might also contain inhibitory substances, but this we have not yet proved.

SUMMARY AND CONCLUSIONS

Adrenaline chloride injected intraperitoneally into 14 suckling rats strikingly inhibited the normal proliferative activity of the cells of the adrenal medulla as compared with that of 7 controls. Others have shown by both histological and chemical methods that the artificial administration of epinephrine inhibits the secretion of this substance by the chromaffine cells of the adrenal. Excess of secretion therefore not only inhibits the function of the individual cell but it prevents the formation of new cells.

Since positive stimuli speeding the proliferation of cells have been demonstrated both in vitro and in the living animal it may be assumed that in the automatic regulation of proliferative activity both inhibition and stimulation play a part.

The only other histological changes observed following the epinephrine injections were minute foci of necrosis in the wall of the left ventricle. Previously adrenaline myocarditis has been produced with difficulty in animals other than the rabbit. These necroses show that the toxic effect of epinephrine on the myocardium is not peculiar to the rabbit.

REFERENCES

1. Drummon, W. B.: J. Physiol. **31**: 81. 1904.
2. Fleisher, M. S. and L. Loeb: Arch. Int. med. **3**: 78. 1909.
3. Samson, P. C.: Arch. Path. **13**: 745. 1932.
4. Ogata, T. and A. Ogata: J. Exper. Med. **25**: 807. 1917.
5. Cramer, W.: Brit. J. Exper. Path. **7**: 88. 1926.
6. McJunkin, F. A. and B. D. Roberts: Proc. Soc. Exper. Biol. & Med. **29**: 893. 1932.
7. McJunkin, F. A., W. R. Tweedy and H. C. Breuhaus: Arch. Path. In press.
8. Tournade, A. and M. Chabrol: Compt. rend. Soc. de biol. **94**: 535. 1926.
9. Carrel, A.: Proc. Inst. Med., Chicago, **8**: 62. 1930.
10. McJunkin, F. A. and T. Matsui: Arch. Path. **12**: 794. 1931.
11. McJunkin, F. A. and H. C. Breuhaus: Arch. Path. **12**: 900. 1931.

AN EXPERIMENTAL ANALYSIS OF CERTAIN PITUITARY-ADRENAL-GONAD RELATIONSHIPS*†

WAYNE J. ATWELL
Department of Anatomy, University of Buffalo
BUFFALO

Among the results of experimental hypophysectomy in mammals are loss of weight, or, in the case of young animals, failure to increase in weight; loss of libido sexualis, cessation of estrus, or sexual infantilism; lessened spontaneous activity, lowered metabolism and lowered temperature (14, 7, 12). In amphibia the outstanding external features are a silvery appearance and a failure to undergo metamorphosis (1, 13).

Autopsy of the hypophysectomized mammal shows atrophy of the thyroid, adrenal cortex, gonads and secondary sex organs, the thymus, and to a certain extent the kidneys, liver and spleen (15).

It is apparent that the hypophysectomized animal is characterized not alone by absence of the pituitary but also by a marked reduction in size, and presumably also in function, of several other highly important endocrine glands.

In attempting to analyze this fairly complex symptomatic and glandular situation from an endocrine viewpoint it becomes important to determine what effects are due primarily to absence of the hypophysis and what secondarily, through impairment of the thyroid, the adrenal cortex, or the gonads.

The rôle of the thyroid in relation to amphibian metamorphosis has been rather definitely established by the following observations: (1) anterior pituitary substance given to hypophysectomized tadpoles stimulates the atrophic thyroid and induces metamorphosis; (2) thyroid substance to hypophysectomized tadpoles produces metamorphosis; (3) pituitary substance to hypophysectomized tadpoles which also have been thyroidectomized does not cause metamorphosis. It is clear that the hypophysis works through the thyroid in this particular reaction.

Likewise, the restoration of the basal metabolic rate of hypophysectomized rats by hypophysial implants is believed by Foster and Smith (7) to be due to repair of the thyroid, since thyroid administered alone raises the metabolic rate in this condition.

The comparative sensitivity of the uteri and vaginae of hypophysectomized and of ovariectomized rats to injections of follicular hormone has been studied recently by Smith (16). No essential difference was found.

*Aided by a grant from the Carnegie Corporation to the Carnegie Institution of Washington.

†Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 10, 1932.

The responses of both organs were always as great and not infrequently greater in animals which had been hypophysectomized than it was in those which had been ovariectomized. These and other experiments have failed to show any direct interrelationship of the vagina or utĕrus with the anterior hypophysis.

The functional relationships of the adrenal cortex in the above pictured syndrome are by no means so well known. We well may ask what symptoms and what glandular deficiencies, if any, are secondary to the atrophy of this important endocrine gland following removal of the pituitary.

A great deal of our difficulty is due to the unsatisfactory condition of our knowledge concerning the normal function of the adrenal cortex. There seems to be considerable clinico-pathological and some experimental evidence for believing that the adrenals are related to sexual development and activity. Among the former may be recalled the following: (1) the well-known relation of hypernephroma and sexual precocity, hirsuitism or virilism; (2) the fact that the cortex is larger in the female and that it becomes hypertrophied during pregnancy: (3) the cortex is ill-developed in sexual deficiency; (4) changes occur in the cortex during the estrous cycle of many animals—in the frog, for example, during the mating season it is said to become greatly enlarged, and to undergo regression afterward; (5) after castration the cortex is said to be hypertrophied (10).

Among recent experimental studies the following may be mentioned: Nice and Shiffer (11) report early opening of the vagina in 6 of 10 rats which survived multiple adrenal transplants. Corey and Britton (5) induced precocious sexual maturity in the rat (as judged from the condition of the ovaries) by injections of cortico-adrenal extracts. There also was hypertrophy of the hypophysis in 20-day rats. These authors suggest that the cortical extract acts through the medium of the hypophysis. Freed, Brownfield and Evans (8) report degeneration of the testis following adrenalectomy in the white rat, either mature or immature. Martin (9) has found that complete suprarenalectomy in the female rat suppresses or makes irregular the oestrous cycle. Transplants of adrenal cortex maintained normal health, body weight and ovarian activity. Martin also holds that the adrenal acts on the ovary through the mediation of the hypophysis.

As throwing light on the pituitary-adrenal relationship a recent note by Evans, Meyer, Pencharz and Simpson (6) is of interest. These authors record the remarkable, prompt and uniform relief from the cachectic state (of hypophysectomy) following the administration of purified growth-hormone extracts. "Not only is growth resumed but a rapid and impressive change in the constitutional state of these animals results. This is indicated especially by the resumption of normal turgor to their tissues and, above all, of normal muscular strength and tone. The myasthenia so characteristic of the hypophysectomized animals disappears within 10 days following the growth hormone therapy." Autopsy shows repair of both the

thyroids and the adrenals. "In the adrenal of the treated animals the cytoplasm of the cortical cells is restored and three zones become again distinguishable. The gonad-stimulating hormone, on the contrary, has no influence on the cachexia, and produces no such repair in adrenals, even though a dose is administered which causes excessive hypertrophy of the gonads."

These authors further suggest that "It is quite probable that the cachectic state and the adrenal atrophy are causally interrelated and that it is to the change in the adrenal following administration of the growth hormone that we must refer the remarkable general constitutional restoration."

OBSERVATIONS

Our experiments were undertaken to determine what repair, if any, is produced by administration of potent cortical adrenal extract to the hypophysectomized animal. It was believed that such a procedure might prove of value in showing, not alone something of the interrelationships of these two glands, but also might give a clue to the normal function of the suprarenal cortex. Begun somewhat over a year ago these experiments have included amphibian, and more recently, mammalian material. A preliminary report of the amphibian work has been given (3).

AMPHIBIAN EXPERIMENTS

The amphibian used was the wood frog, Rana sylvatica. The hypophysis was removed when the animal was in the tailbud stage. At different ages thereafter groups of animals were given daily 0.05 cc. of cortin (cortical adrenal extract, Hartman) by intraperitoneal injection, using special fine hypodermic needles. Females treated for a period of about two months beginning at five months of age showed a definite stimulation of the ovaries. Younger animals treated for periods of two or three weeks did not exhibit this effect. The ovaries of treated animals averaged two to two and a half times the size of those from hypophysectomized untreated controls, as determined by quantitative methods.

Histologically, untreated animals show ovaries with large ovocytes in the central part of the gland but with much interstitial tissue and a cortex which appears to be relatively quiescent in that it consists of many ovogonia and only a small number of ovocytes. The ovaries of treated animals, on the other hand, are distended with many large ovocytes located in the cortex as well as centrally. The interstitial tissue and the residual nests of ovogonia in the cortex are reduced to relative insignificance. The whole histological picture is that of recent enlargement of numerous ovocytes in the cortex of the gland. It is significant that this stimulation has taken place in the entire absence of the pituitary. There was no effect on pigmentation, growth or differentiation or upon the thyroid gland. The effect on the male gonad has not been studied.

MAMMALIAN EXPERIMENTS

In the mammalian experiments albino rats weighing from 150-200 grams, principally from the Wistar experimental colony strain, were used. The hypophysis was removed by the parapharyngeal route according to the method devised by Smith (15), with certain modifications introduced by Richter and Wislocki (12). These operators substitute two sizes of round dental burs, motor driven, for the hand-operated trephine of Smith.

Immediately following the operation the animal was given 2-10 cc. of warm physiological salt solution subcutaneously. It was then kept warm until recovery was complete. Later it lived in a warm (75-80° F.), constant temperature room. Beginning about the sixth day following the operation certain animals received daily two injections of cortin, one at 8 a.m. and the other at 8 p.m. In the first series the dosage was 0.5 cc. per injection. Other operated animals were injected at similar times with an equal amount of salt solution. Still other litter mates, unoperated, were available as controls. In a second series the dosage was increased to 2 cc. per injection. Periods of treatment and of non-treatment were alternated.

The operated animals were weighed daily and daily vaginal smears obtained from the females. In the latter part of the experiment with the first series and for all the time of the second series, spontaneous activity cages, which recorded revolutions, were available and the animals lived in them. The rats of Series 1 were killed from four to eight weeks following operation after having received treatment for from three to seven weeks. Unoperated litter mates were killed at the same time. At the autopsy gonads, genital tract exclusive of gonads, adrenals, thyroid, thymus, liver, spleen and kidneys were carefully dissected out, weighed, and fixed in Bouin's fluid for histological study. The hypophysial region also was preserved, decalcified and sectioned serially. This procedure was deemed necessary in all cases to prove the success or failure of the operation. Twenty rats were hypophysectomized. Nine of these have received cortical extract.

Weights, ages and organ weights for a typical hypophysectomized, cortin-treated female and a similar male of Series 1, each with two controls, are shown in Table 1. To those familiar with Smith's data, it will be apparent that the cortin treatment has not restored the weight of gonads, thyroids or adrenals, nor indeed of any of the organs studied.

Likewise histological examination of these glands fails to reveal any repair. In all respects these exhibit, unmodified, the changes which have been shown to be the typical results of hypophysectomy.

The interrupted oestrous cycles of the females were not restored.

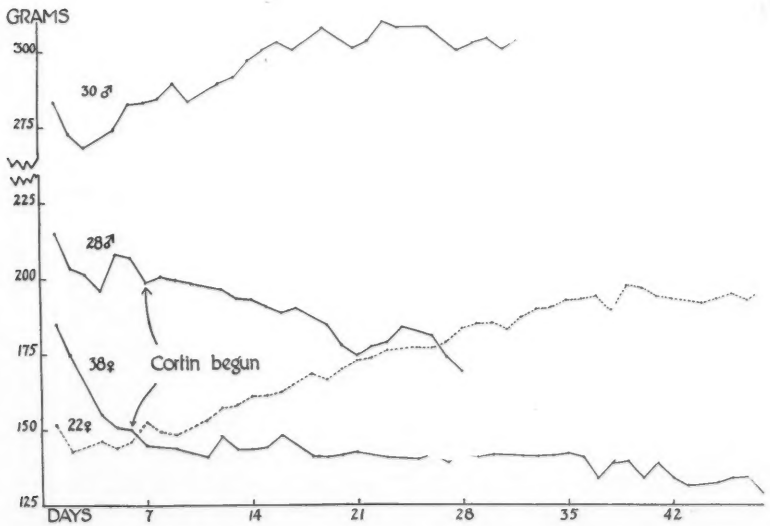
Growth curves of these typical animals, each with an essentially normal control, are shown in graph 1. It will be seen that no restoration of the growth rate has occurred.

TABLE I

Ages and Weights

	Experiment Begun		Experiment Terminated											
						Absolute Weight of Organs								
	Age, Days	Weight, Grams	Age, Days	No. of Days After Exper. Began	Weight, Grams	Gonads	Genital System Exclusive of Gonads	Adrenals	Thyroid	Thymus	Kidneys	Spleen	Liver
FEMALE RATS													
H 38—Hypophysectomized + Cortin....	158	185	214	56	129	0.026	0.191	0.014	0.008	0.072	0.909	0.293	4.775
H 37—Control.....	158	....	214	56	210	0.084	0.767	0.056	0.027	0.226	1.114	0.407	7.975
H 41—Control.....	....	....	....	....	200	0.053	.....	0.066	0.040	0.048	1.596	0.568	8.522
MALE RATS													
H 28—Hypophysectomized + Cortin....	156	215	184	28	168	0.487	0.808	0.010	0.011	0.031	1.165	0.846	5.084
H 30—Control (Unsuccessful operation)	157	284	187	30	304	3.414	2.847	0.039	0.017	0.155	2.480	0.577	13.617
H 32—(Unsuccessful operation + Cortin)	157	247	212	55	255	2.132	3.523	0.022	0.015	0.090	1.617	1.898	9.058

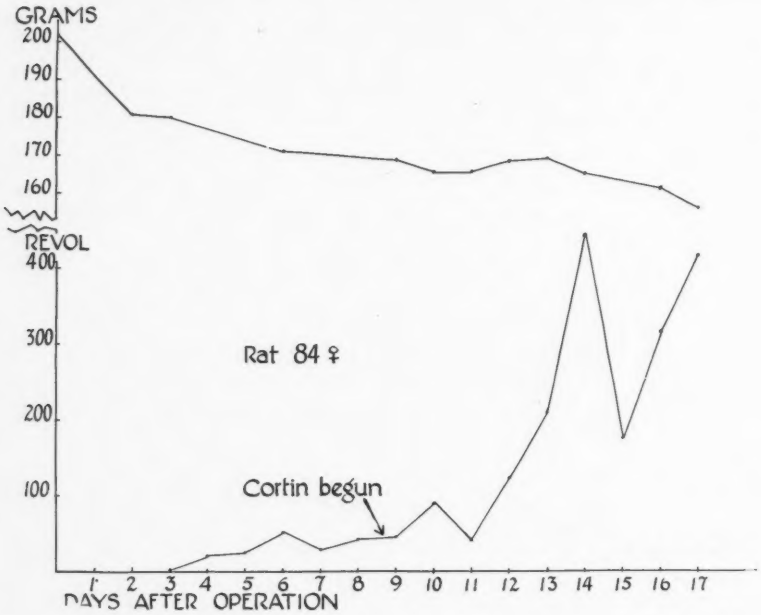
Table 1. Showing ages and weights of typical male and female rats which were hypophysectomized and treated with injections of 0.5 cc. cortin twice daily. Each is accompanied by records of control animals. Cortin treatment has not restored the weights of any of the organs examined.



Graph 1. Shows the weight records of Rats 28 and 38, which were hypophysectomized and treated with cortin, and of Rats 22 and 30, which were unsuccessfully operated upon and which serve as essentially normal controls. In spite of the cortin treatment Rats 28 and 38 continued to lose weight in a manner typical of the hypophysectomized animal.

In certain respects, however, the cortin-treated rats were strikingly different from untreated animals. Instead of being the cold, apathetic and almost entirely inactive little beasts which hypophysectomized animals characteristically are, they were distinctly active and showed a body temperature approaching normal. Of Rat 38 (Series 1), whose movements were for a time recorded in a spontaneous activity cage, caretakers often remarked, "What a lively little creature that rat is!"

Graph 2 shows the spontaneous activity of Rat 84 (Series 2) for a period of non-treatment followed by a period of cortin injection. After



Graph 2. Showing increased spontaneous activity of hypophysectomized Rat 84, following injections of 2 cc. of cortin twice daily. The upper line of the graph shows a continued decrease in weight.

treatment is begun it requires two or three days for the effects to become apparent. Although cortin treatment produces a definite effect on spontaneous activity it does not restore that activity to normal. Many of our rats before operation have produced several thousand revolutions of the cage in twenty-four hours.

With the rats of Series 2 rectal temperatures were taken at the same hour each day. Rat 81 had a mean temperature of 99.7° F. for an eight-day period of treatment and a mean of 99.0° for the following eight-day period of non-treatment. If, however, the readings for the first three days of each period are not considered (this being the time required for maximum effects to become apparent) the means are 100.0° and 98.65° for the

periods of treatment and non-treatment, respectively, with a difference of 1.35° F. Mean temperatures of other periods show differences of 0.7-0.9° in favor of the treatment periods. During this same sixteen days an unoperated control (Rat 87, male) showed an average temperature of 101.4° F. This figure is somewhat higher than usual, due to the struggling of the animal on two or three occasions at which the temperature rose above 102°. The minimum reading, however, was never under 100° F.

DISCUSSION

The reparation of asthenia, hypothermia and spontaneous activity which follows cortin treatment is accomplished without apparent restoration of any endocrine gland examined. This adds weight to Hartman's belief that cortin acts directly upon various tissues of the body. It must be admitted, however, that the islands of the pancreas have not been studied in this relationship.

Calder (4) has pointed out that many cases of Simmonds' disease are probably incorrectly diagnosed as Addison's disease. It would seem that the symptoms of hypotension and asthenia observed in Simmond's disease are not attributable directly to pituitary insufficiency but to secondary involvement of the suprarenal cortex. We shall await with interest the therapeutic test using a potent cortical extract in this condition. The observations here recorded provide an experimental basis for the expectation that cortical extract will relieve the asthenia, hypothermia, and presumably also the hypotension of Simmond's disease as it does in experimental hypophysectomy.

These experiments likewise provide a necessary link in the evidence that the relief of myasthenia which follows administration of hypophysial growth hormone to hypophysectomized rats [Evans and co-workers (6)] probably results from activation of the adrenal cortex.

We have not been able, with the dosage and length of treatment so far employed, to induce repair of the hypoplastic gonads in the rat. The experiment is being continued with increased doses.

SUMMARY

1. Injection of a potent cortical adrenal extract (cortin, Hartman) over a period of two months, beginning at five months of age, stimulated the ovaries of hypophysectomized tadpoles of Rana sylvatica. Such ovaries averaged nearly two and one-half times the size of ovaries from untreated hypophysectomized controls.

2. Twenty rats were hypophysectomized by the parapharyngeal route. Nine of these were injected subcutaneously twice daily with cortin in doses varying from 0.5 cc. to 2 cc. per injection. This treatment partially relieved the characteristic asthenia and hypothermia and partially

restored spontaneous activity, without any apparent reparation of the atrophic thyroid, adrenals or gonads, and without any effect upon growth.

REFERENCES

1. Allen, B. M.: Science, **44**: 755. 1916.
2. Allen, B. M.: Proc. Soc. Exper. Biol. & Med. **27**: 35. 1929.
3. Atwell, W. J.: Proc. Soc. Exper. Biol. & Med. **29**: 621. 1932.
4. Calder, R. M.: Bull. Johns Hopkins Hosp. **50**: 87. 1932.
5. Corey, E. L. and S. W. Britton: Am. J. Physiol. **99**: 33. 1931.
6. Evans, H. M., K. Meyer, R. Pencharz and M. E. Simpson: Science, **75**: 442. 1932.
7. Foster, G. L. and P. E. Smith: J. A. M. A. **87**: 2151. 1926.
8. Freed, S. C., B. Brownfield and H. M. Evans: Proc. Soc. Exper. Biol. & Med. **29**: 1. 1931.
9. Martin, S. J.: Am. J. Physiol. **100**: 180. 1932.
10. McLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, 6th Ed., p. 980. The C. V. Mosby Company, St. Louis. 1930.
11. Nice, L. B. and A. L. Shiffer: Endocrinology, **15**: 205. 1931.
12. Richter, C. P. and G. B. Wislocki: Am. J. Physiol. **95**: 481. 1930.
13. Smith, P. E.: Science, **44**: 280. 1916.
14. Smith, P. E.: J. A. M. A. **88**: 158. 1927.
15. Smith, P. E.: Am. J. Anat. **45**: 205. 1930.
16. Smith, P. E.: Am. J. Physiol. **99**: 349. 1932.

FURTHER STUDIES ON ESTRIN-HYPOPHYSEAL ANTAGONISM IN THE WHITE RAT

JACK SPENCER, FRED E. D'AMOUR AND R. G. GUSTAVSON*
From the Research Laboratories, University of Denver
DENVER

Moore and Price (1) have advanced the theory that injections of gonadal hormones inhibit the hypophysis as regards production of the gonad-stimulating factor and thereby explain the degeneration of the gonads following injection of estrin and the male sex hormone. The authors (2) (3) have studied the effects of estrin administration on the growth rate and found that young rats injected daily with 20 rat units of estrin did not grow as rapidly as did their litter mate controls. They also made histological studies of the gonads and confirmed the findings of Moore and Price; the gonads did not develop normally but remained small and infantile. The authors further found that the damage done was not permanent; prompt recovery both in growth and gonadal function occurred following cessation of the injections.

In the present study we desired to determine whether the effects of estrin injections could be overcome by the use of appropriate hormones, that is, whether the simultaneous injection of the growth-promoting hormone from the hypophysis would give normal growth, and simultaneous administration of the gonad-stimulating factor from the urine of pregnancy bring about normal gonadal development. We have adopted the name "hebin," suggested by Lawrence and van Dyke, to designate the gonad-stimulating factor obtained from pregnant urine, leaving the question open as to whether this represents either one or the other or both Prolan "A" or Prolan "B."

Since these hormone preparations were crude and we anticipated having to use rather large amounts over a long period of time, we did not attempt to obtain as great a degree of inhibition as in our previous work, and, therefore, injected only ten units of estrin instead of twenty.

PROCEDURE

Eighty rats, between three and four weeks of age and just weaned, were divided as nearly as possible into four groups, the sexes in each group being kept separated. The first group received daily injections of ten rat units of estrin only. The second group received the same amount of estrin and in addition received injections of hebin. The third group received, in addition to estrin, injections of the growth hormone of the hypophysis.

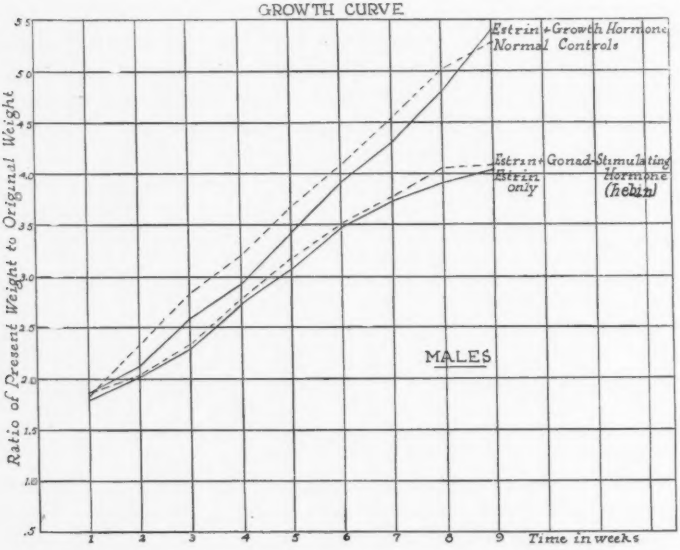
*The present investigation was aided in part by the Committee for Research in Problems of Sex of the National Research Council.

The fourth, or control, group received no injections. Care and feeding of all groups was identical. All animals were weighed each week. The experiment ran nine weeks from the time injections were commenced.

Preparation of Hormones: The estrin was prepared from pregnancy urine, according to the method described by us (4), except that the final sublimation was omitted and the preparation was therefore not crystalline. It was of such potency that 5 gamma represented one rat unit when assayed according to the Coward-Burn method as repeated by us (5). It should be noted that the Coward-Burn unit represents considerably more estrin than does the Allen-Doisy unit. Our experience indicates that one Coward-Burn unit is equivalent to about twelve Allen-Doisy units.

Hebin was obtained from human pregnancy urine according to the method used by Lawrence and Van Dyke (6). The urine was made acid to Congo Red with acetic acid, concentrated to one-fifth its volume (at room temperature), four volumes of 95 per cent alcohol added and the precipitate filtered off after frequent shaking and standing. The precipitate is washed with alcohol and ether, dried, re-dissolved in water and re-

GRAPH I



precipitated. The final preparation was assayed on immature rats; one-tenth cc. injected twice per day for five days induced maturation of the ovaries. The rats in group II received one-half cc. of this preparation every other day throughout the experiment.

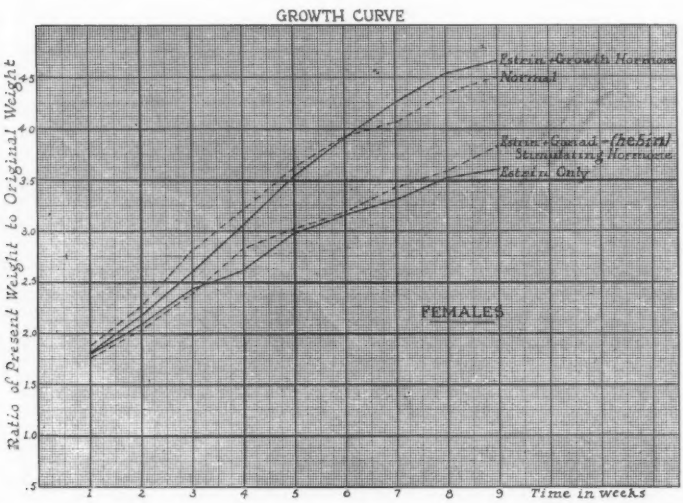
The growth hormone was prepared according to the method of Evans (7). This is an alkaline extract of finely ground beef anterior lobes. It

was assayed according to the method described by him and was of such potency that injection of one cc. per day for twenty days into a series of six mature female rats gave an average increase of 44 grams per rat. During the first six weeks of the experiment the animals comprising group III received one cc. of this extract every other day, the dosage was then increased to one cc. every day for the remaining three weeks.

RESULTS

Curves representing the rates of growth are shown in graphs I and II. It will be noted that the growth rates of the rats receiving hebin prac-

GRAPH II



tically parallel those of the rats receiving estrin only, indicating that there is no growth hormone in pregnancy urine, or at least that none is present in the preparation obtained by the methods used. The growth rates of the animals receiving growth hormone in addition to estrin lag somewhat behind the normal controls during the first part of the experiment. The dosage was doubled at the end of the sixth week and there is a prompt rise in the curve, especially evident in the case of the females.

We have previously shown (3) that the bones of estrin-injected animals are consistently shorter than their controls. Similar measurements were made in the present experiment and comparable results obtained. We had expected that the lengths of the bones of the group receiving growth hormone would show an approximate agreement with the control group since their growth rates as measured by weight were so nearly

equal. As will be seen from Table I this expectation was not realized, although in most instances the bone lengths of this group are somewhat greater than those receiving estrin only.

TABLE 1

AVERAGE SKULL MEASUREMENTS

	Females		
	Condylo-Basilar Length	Condylo-Palatal Length	Zygomatic Width
	mm.	mm.	mm.
Estrin only	38.7	21.9	19.6
Estrin plus growth hormone	39.4	22.1	20.0
Normal	40.0	22.7	20.2
	Males		
Estrin only	39.4	21.8	19.9
Estrin plus growth hormone	40.1	22.5	20.7
Normal	40.7	22.9	20.9

AVERAGE LEG BONE LENGTHS

	Females			
	Femur	Humerus	Ulna	Tibia
	mm.	mm.	mm.	mm.
Estrin only	27.5	21.6	25.3	31.1
Estrin plus growth hormone	28.9	21.9	25.2	32.0
Normal	29.3	22.7	26.2	32.9
	Males			
Estrin only	28.6	22.4	25.7	30.0
Estrin plus growth hormone	29.7	23.3	26.3	33.6
Normal	31.1	24.0	26.8	35.1

The effects upon gonadal development are shown in Table 2. It will be noted that the weight of the testes in the group receiving hebin is twice that of the estrin group, while still only one-half that of the controls. The histological picture, however, shows a functional development approaching that of the controls. The seminal vesicles of the group receiving hebin, although nearly twice as large as the estrin group are much smaller than those of the control group. The ovaries of the animals re-

TABLE 2

AVERAGE WEIGHT OF GONADS

	Males		Females	
	Testes	Sem. Ves.	Ovaries	Uterus
Estrin only	.50	.12	.06	.31
Estrin plus hebin	1.08	.20	.13	.34
Estrin plus growth hormone	.47	.10	.09	.29
Normal controls	2.32	.58	.13	.45

ceiving hebin in addition to estrin have the same average weight as do the controls; they are more than twice as heavy as those receiving estrin only. The effect upon the uterus was very slight.

Histological study of the reproductive organs showed in the case of the estrin-injected males, testes similar in all respects to previous findings. They have small tubules and show no evidences of advanced spermatogenesis. The testes of the animals receiving hebin in addition showed apparently normal spermatogenesis, live sperm were demonstrated in the vasa of these animals and although the tubules are smaller and sperm are not present as abundantly as in the controls, the testes are obviously functional. The seminal vesicles of this group show an epithelium approaching that of the controls as contrasted with the castrate type of epithelium occurring in the estrin-injected group.

The ovaries of the group receiving estrin plus hebin were apparently normal, developing follicles as well as many corpora lutea being present. Plates I and II show representative sections of the gonads of each group.

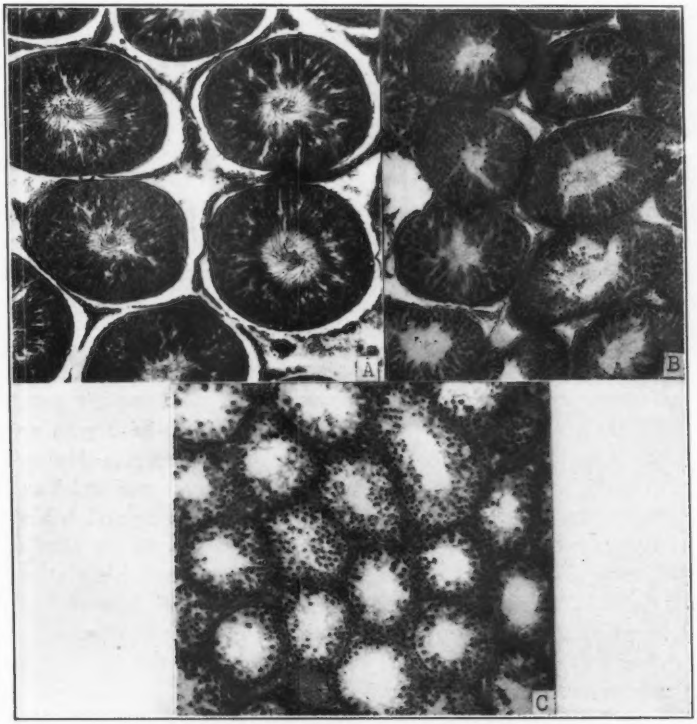


Figure 1. Cross-section through testis of rat
(A) Normal
(B) Estrin-injected
(C) Estrin-injected plus hebin

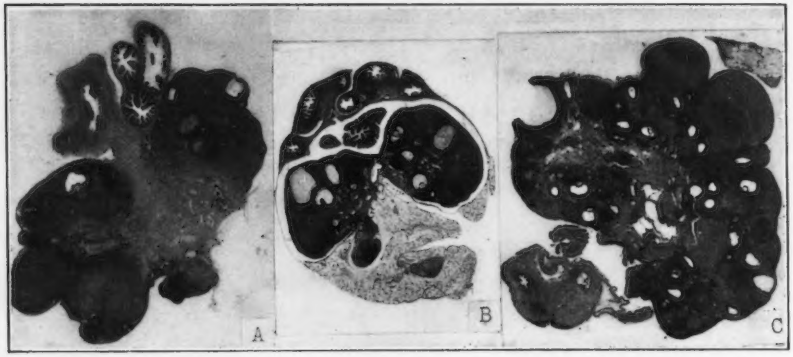


Figure 2. Cross-section through ovary of rat
(A) Normal
(B) Estrin-injected
(C) Estrin-injected plus hebin

DISCUSSION

The results obtained in this study raise several questions which cannot be answered without further investigation. First is the question of bone growth, which, as was noted, did not keep pace with the weight increase. Evans assays growth hormone preparations by their effect in increasing the weight of mature animals, animals which, as he states it, have reached their "plateau." We do not know whether animals which have had their weights increased by the administration of growth hormones after reaching maturity would show an increased length of the bones but would be inclined to doubt that possibility. It is quite possible that increased dosage early in the experiment would have brought about an increase in bone length which in the end would have been comparable to the bone lengths of the control animals.

Conclusions as to what the effects of the hebin or growth hormone injections alone would have been are not valid inasmuch as their action was counterbalanced by the estrin which, presumably, was having an opposite effect. It is nevertheless interesting to note that the results obtained here are, in general, in agreement with the findings of Lawrence and Van Dyke as to the relative effects of hebin as obtained from urine and hebin from the hypophysis. Since our growth hormone was merely an alkaline extract of hypophyses it no doubt contained some gonad-stimulating hormone as well. The amount per cc. was no doubt small, inasmuch as beef glands were used, but continued over such a long time might be expected to have had some effect. Since the animals receiving urinary hebin showed sex glands essentially normal we can conclude that this substance acted equally well on both sexes. There is a difference, however, in the effects of the hypophyseal hebin undoubtedly present in the growth hormone preparation. It will be noted that this hormone had no effect upon the

weight of the male gonads, whereas it did have a considerable effect upon the size of the ovaries.

The behavior of the accessory sex glands is difficult to understand. Inasmuch as the action of urinary hebin upon the immature seminal vesicle is very great, this being used as one method of assay of hebin preparations, we naturally expected the size of the vesicles of this group to be very much greater. It is possible, judging by the fact that testes also did not reach the normal size that our dosage was low—insufficient, in fact, to overcome entirely the effect of the estrin. In the case of the uterus we are at a loss to explain the findings. We had originally expected to find relatively enormous uteri as the result of estrin injections alone and when this did not occur, expected the cause, whatever it might be, of uterine inhibition to be overcome by the use of one or the other of the two hormones used. This also failed to be demonstrated. We find the size of the uteri in all three of the injected groups to be approximately the same and all are approximately one-third lighter than those of the control group.

We do not believe that the results of this experiment definitely prove that the effects resulting from continued estrin injections are due to inhibition of the hypophysis, but we do believe that it is difficult to suggest any other theory that would explain the results more satisfactorily. It is, of course, reasonable to suppose that inhibition of growth and inhibition of gonadal development from any cause (a cause not necessarily associated with the hypophysis in any way whatever) might be overcome by the use of the appropriate hypophyseal hormone, but it is difficult to imagine what the action of estrin would be in bringing about such inhibition. It can hardly be due to toxic action since the other two preparations were quite crude and contained large amounts of impurities, any of which might, with equal justice, be expected to be toxic. In the present state of our knowledge we are willing to accept the Moore-Price theory as a reasonable one.

SUMMARY

The purpose of this investigation was to discover whether the inhibitory effects of continued estrin injections upon the growth and gonadal development of young rats could be overcome by the simultaneous injection, in the one case, of the growth factor from the hypophysis, and, in the other, by simultaneous injection of urinary hebin.

Injection of the growth factor of the hypophysis, prepared according to the method of Evans, along with ten rat units of estrin, gave growth curves approximately paralleling those of normal controls. The average bone lengths were, however, not as great as the controls, although in general greater than those receiving estrin only.

Simultaneous injection of hebin prepared after the method of Lawrence and Van Dyke resulted in apparently functional gonads. The average weight of the testes was double that of the animals receiving estrin

only, but only half that of the control animals. The ovaries of the animals receiving hebin plus estrin weighed as much as the controls and twice as much as those receiving estrin only.

From this evidence the authors are inclined to accept the theory of Moore and Price that the action of estrin in inhibiting growth and gonadal development is by way of inhibition of the hypophysis, although not considering the theory as definitely proven.

REFERENCES

1. Moore, C. R. and D. Price: Proc. Soc. Exper. Biol. & Med. **28**: 1. 1930.
2. Spencer, Jack, R. G. Gustavson and F. E. D'Amour: Proc. Soc. Exper. Biol. & Med. **28**: 500. 1931.
3. Spencer, Jack, F. E. D'Amour and R. G. Gustavson: Am. J. Anat. **50**: 1. 1931.
4. D'Amour, F. E. and R. G. Gustavson: J. Pharmacol. and Exper. Therap. **40**: 485. 1930.
5. D'Amour, F. E. and R. G. Gustavson: **40**: 473. 1930.
6. Lawrence, Z. W. and H. B. Van Dyke: J. Pharmocal. Exper. Therap. **43**: 93. 1931.
7. Evans, H. M. and M. E. Simpson: Am. J. Physiol. **98**: 3. 1931.

THE INFLUENCE OF OESTRIN ON THE GONAD-STIMULATING COMPLEX OF THE ANTERIOR PITUITARY OF CASTRATED MALE AND FEMALE RATS†

ROLAND K. MEYER*, S. L. LEONARD,
FREDERICK L. HISAW AND S. J. MARTIN

From the Department of Anatomy, University of Rochester, School of Medicine and Dentistry and the Department of Zoology, University of Wisconsin

The results of the researches of Smith and Engle (1927), Zondek and Aschheim (1927) and many others have demonstrated the dependence of the function of the gonad upon the anterior pituitary gland. One very characteristic quality of the function of the gonad, the ovary in particular, is its rhythmical activity. This quality suggests a parallel activity in the anterior pituitary and the probability of pituitary-gonadal interrelationship. Such a relationship was first suggested by Engle (1929a) in the publication of his study on the gonad-stimulating hormones of the anterior pituitary of the gonadectomized rat in which he stated that the release of gonad-stimulating complex from the anterior pituitary depended upon the presence of the gonad (ovary). In a more recent publication he has discussed the evidence supporting this idea and indicated that the oestrous hormone may be the factor which effects the release of the gonad-stimulating complex (Engle, 1931).

An important and interesting approach to the study of the ovary-pituitary relationship is the influence of the oestrous hormone on the amount of the gonad-stimulating hormones in the anterior hypophysis. Burch and Cunningham (1930) reported that injections of the oestrous hormone (from human placenta) into castrated female rats produced an increase in the amount of the gonad-stimulating hormone of the hypophysis as determined by implantation of this gland into immature female mice. Later we (Meyer, Leonard, Hisaw and Martin, 1930) published the preliminary results obtained by injecting oestrin (Amniotin) into castrated male and female adult rats. Our source of oestrin was different from that of Burch and Cunningham and the period of injection was longer. The test animals used in our experiment were rats. We obtained data which indicated that oestrin decreased the gonad-stimulating power of the hypophyses of castrated rats when compared with the hypophyses of non-injected castrated animals.

Since the publication of this preliminary note we have obtained additional data relative to what we designate as the influence of "long period

†The investigation done at Wisconsin was aided in part by a grant, administered by Dr. F. L. Hisaw, from the Committee for Research in Problems of Sex of the National Research Council.

*National Research Council Fellow in the Biological Sciences.

injections of the oestrous hormone'' on the gonad-stimulating power of the hypophyses of castrated male and female rats. It is the object of this report to present the data which we have obtained from such an experiment.

EXPERIMENTAL PROCEDURE AND RESULTS

The animals used in this investigation were male and female albino rats of two Wistar Institute strains. The diet of one group was a synthetic one known to contain the necessary vitamins and foodstuffs. The other group was fed on a diet consisting of table scraps supplemented with cod-liver oil and lettuce. The variation in diet and laboratory conditions did not contribute any differences in the data obtained from either group. Engle (1929a) and Evans and Simpson (1929) and others have shown that the hypophysis of the castrated male or female rat is considerably more potent than that of the non-castrated animal. This increase in potency they conclude is a result of an increase in stored gonad-stimulating hormones in the gland. We castrated all animals used as donors before the beginning of the period of injection. The number of days elapsing between the castration and the beginning of injection varied from 1 to 90 days and the length of the injection period varied from 13 to 37 days. The oestrogenic substances used were Amniotin and Theelin* which were restandardized to check the manufacturers' statements of potency. The products were administered in an oily solution (Amniotin) or an emulsion (Theelin), the dosage of which varied from 4 to 10 rat units per rat per day. Certain control animals were injected daily with the same amount of Mazola oil (maize derivative) as that which the experimental animals received. Control animals and experimental animals were killed by decapitation at the end of the injection period and their hypophyses (anterior and posterior lobes) were implanted in the leg muscles of immature female rats varying in age from 18 to 28 days. In some instances two glands were implanted. The number of control donor glands implanted always equalled the number of glands from the experimental animals of the corresponding group. Whenever possible the weight of the experimental donor (or the combined weight of two animals) was selected to come within a range of 20 grams plus or minus the weight of the control donor. All immature recipients were killed on the morning of the sixth day after implantation and the ovaries were carefully dissected free from extraneous tissues and weighed in a stoppered weighing bottle to exclude error from evaporation. All computations of weight differences were made per litter and expressed as the percentage by which the ovaries of the experimental recipients were less than those of the control recipients which were taken as one hundred per cent. The vagina, uterus and ovaries were fixed in Bouin's fluid and a microscopical study was made of the ovaries of representative control and experimental animals.

*We are very thankful to E. R. Squibb and Sons for supplying us with Amniotin and to Parke, Davis & Co. for the Theelin.

The general results of the investigation are summarized as follows:

Total number of donors (male and female) 78
Total number of recipients 64
Average weight of the ovaries of the "control male" recipients .... = 35.08 mgm.
Average weight of the ovaries of the "experimental male" recipients ..... = 19.18 mgm.
Average that the "experimental male" recipients' ovaries weighed less than "control male" recipients' ovaries ..... = 45.33%
Average weight of the ovaries of the "control female" recipients ... = 22.16 mgm.
Average weight of the ovaries of the "experimental female" recipients ..... = 12.78 mgm.
Average that the "experimental female" recipients' ovaries weighed less than "control female" recipients' ovaries ..... = 46.84%
Average of all "control (male and female)" recipients' ovaries .... = 28.24 mgm.
Average of all "experimental (male and female)" recipients' ovaries. = 16.56 mgm.
Average that the "male and female experimental recipients" ovaries weighed less than the "control male and female" recipients' ovaries ..... = 41%

(The detailed and specific data for each donor and recipient are included in Table I.)

Histological study of the ovaries of the recipients showed that the control ovaries contained more corpora lutea and follicles than those of the experimental animals. These results are contrary to those of Kraul (1931), who found that treatment of the donors (rabbits, guinea pigs and mice) with oestrin and placental and corpus luteum extracts produced more corpora lutea in the ovary of immature experimental recipients than in those of the control recipients.

DISCUSSION

The results which we have obtained demonstrate that oestrin (Amniotin, Theelin) in the amounts given prevents the increase in the gonad-stimulating power of the hypophysis which normally follows castration. Our data are not extensive enough at the present time to allow us to come to other than this definite conclusion. However, the data are, in certain respects, sufficient to point out other probabilities, as for example, the decrease in the potency of the hypophysis is not proportional to the amount injected or the length of the injection period.

Evans and Simpson (1929) have shown that the anterior pituitary gains in gonad-stimulating power most rapidly in the first three weeks of the castration period, and from this they conclude that there is a storage of the complex. Our data show that injections of oestrin begun either immediately or soon after castration prevent this increase in potency, and that injections begun at a relatively much later time in the castration period when the increase in potency is well established, cause a decrease in the amount already present. These facts, together with those of Evans and Simpson, we believe, indicate that the oestrin injected after the hypophysis has stored the greatest amount of gonad-stimulating complex, in some way decreases the amount stored before the injection period. These data may be interpreted to mean that oestrin will prevent the increase in

TABLE I

Donors						Recipients				
Rat No.	Sex	Body Wt. (gms)	Castration Period		Oestrin Per Day (r. u.)	Rat No.	Age at Time Implant. (Days)	Weight of Ovaries (mgm.)		Per Cent the Ovaries of Exp. Weigh Less Than Controls
			Duration (Days)	Days Injected				Control	Experimental	
2	F	345	57	30–57	(M)	Z 1/1	27	33		
9	F	260	57	30–57	(M)					
8	F	270	57	30–57	3(A)	Z 1/3	27		13.9	
6	F	335	57	30–57	3(A)					
1	F	280	57	30–57	3(A)	Z 1/4	27		15.1	
10	F	300	57	30–57	3(A)					
3	F	298	57	30–57	3(A)	Z 1/5	27		20.5	51.
4	F	280	57	30–57	3(A)					
54	M	265	32	13–32	(M)	Z 2/1	27	126.5		
55	M	260	32	13–32	(M)					
60	M	230	32	13–32	(M)	Z 2/2	27	100.		
59	M	280	32	13–32	(M)					
56	M	260	32	13–32	3(T)	Z 2/3	27		23.6	
61	M	195	32	13–32	3(T)					
58	M	250	32	13–32	3(T)	Z 2/4	27		15.	
57	M	210	32	13–32	3(T)					
62	M	210	32	13–32	3(T)	Z 2/5	27		43.8	
63	M	255	32	13–32	3(T)					
64	M	230	32	13–32	3(T)	Z 2/6	27		97.	59.5
65	M	240	32	13–32	3(T)					
68	M	263	120			Z 3/1	24	36.5		
72	M	210	120			Z 3/2	24	43.9		
67	M	260	120	91–120	10(T)	Z 3/3	24		19.7	
73	M	257	120	91–120	10(T)	Z 3/4	24		16.9	
74	M	220	120	91–120	10(T)	Z 3/5	24		15.4	
71	M	218	120	91–120	10(T)	Z 3/6	24		13.1	60.
66	M	250	120			Z 4/1	24	30.9		
69	M	251	120	91–120	10(T)	Z 4/2	24		12.9	
70	M	248	120	91–120	10(T)	Z 4/3	24		28.1	33.6
75	M	240	127			Z 5/1	27	46.2		
76	M	230	127	91–127	10(T)	Z 5/2	27		47.8	
77	M	210	127	91–127	10(T)	Z 5/3	27		12.8	
78	M	264	127	91–127	10(T)	Z 5/4	27		11.	47.6

(M)—Mazola oil. (A)—Amniotin. (T)—Theelin.

TABLE I—Continued

Donors						Recipients				
Rat No.	Sex	Body Wt. (gms)	Castration Period		Oestrin Per Day (r. u.)	Rat No.	Age at Time Implant. (Days)	Weight of Ovaries (mgm.)		Per Cent the Ovaries of Exp. Weigh Less Than Controls
			Duration (Days)	Days Injected				Control	Experimental	
100	F	216	60	40–60	(M)	A 63/1	27	21.9		
102	F	250	60	40–60	(M)					
103	F	214	60	40–60	(M)	A 63/2	27	27.5		
104	F	256	60	40–60	(M)					
105	F	248	60	40–60	6(A)	A 63/3	27		12.3	
106	F	242	60	40–60	6(A)					
107	F	203	60	40–60	6(A)	A 63/4	27		23.	20.6
108	F	218	60	40–60	6(A)					
112	F	165	35	2–35	(M)	A 98/1	23	28.2		
114	F	128	35	2–35	(M)	A 98/2	23	21.1		
115	F	183	35	2–35	(M)	A 98/3	23	20.3		
116	F	175	35	2–35	6(A)	A 98/4	23		19.4	
117	F	135	35	2–35	6(A)	A 98/5	23		8.	
118	F	141	35	2–35	6(A)	A 98/6	23		12.6	43.4
122	F	160	30			A 107/1	21	12.8		
120	F	168	30	2–30	4(A)	A 107/2	21		8.3	
121	F	160	30	2–30	4(A)	A 107/3	21		4.3	50.
126	M	178	30			A 109/1	21	10.9		
127	M	176	30			A 109/2	21	18.7		
128	M	184	30			A 109/3	21	12.4		
123	M	182	30	2–30	4(A)	A 109/4	21		6.7	
124	M	185	30	2–30	4(A)	A 109/5	21		7.9	
125	M	178	30	2–30	4(A)	A 109/6	21		6.5	
129	M	188	30	2–30	4(A)	A 109/7	21		9.3	45.
130	M	169	30			A 111/1	18	9.3		
132	M	191	30			A 111/2	18	6.		
133	M	153	30	2–30	4(A)	A 111/3	18		5.8	
136	M	151	30	2–30	4(A)	A 111/4	18		5.	28.9
139	F	125	30			A 112/1	18	17.4		
138	F	130	30	2–30	4(A)	A 112/2	18		12.3	
137	F	135	30	2–30	4(A)	A 112/3	18		12.7	28.1
141	F	165	30			A 106/1	22	14.5		
140	F	160	30	2–30	4(A)	A 106/2	22		9.1	
142	F	170	30	2–30	4(A)	A 106/3	22		9.8	34.5

(M)—Mazola oil. (A)—Amniotin. (T)—Theelin.

TABLE I—Continued

Donors						Recipients				
Rat No.	Sex	Body Wt. (gms)	Castration Period		Oestrin Per Day (r. u.)	Rat No.	Age at Time Implant. (Days)	Weight of Ovaries (mgm.)		Per Cent the Ovaries of Exp. Weigh Less Than Controls
			Duration (Days)	Days Injected				Control	Experimental	
160	M	168	30			A 110/1	19	7.4		
170	M	167	30			A 110/2	19	7.4		
175	M	159	30	2–30	4(A)	A 110/3	19		4.5	
177	M	157	30	2–30	4(A)	A 110/4	19		10.1	0
178	F	200	37			A 167/1	21	29.3		
179	F	212	37			A 167/2	21	18.2		
180	F	220	37			A 167/3	21	21.8		
181	F	222	37			A 167/4	21	12.3		
183	F	194	37	25–37	4(A)	A 167/6	21		11.5	
184	F	210	37	25–37	4(A)	A 167/7	21		12.8	
185	F	213	37	25–37	4(A)	A 167/8	21		11.8	40.6

(M)—Mazola oil. (A)—Amniotin. (T)—Theelin.

potency which follows castration if given early, and will release the stored gonad-stimulating complex if given later.

At the present time we have no direct evidence which indicates by what mechanism the oestrous hormone reacts upon the anterior pituitary. Is the action on one or both of the hormones of the anterior pituitary? If one believes that there is but one gonad-stimulating hormone elaborated by the anterior pituitary, one which causes the formation of both corpora lutea and follicles, then the problem of differential action of oestrin on the gonad-stimulating hormones of the anterior pituitary does not present itself. Perhaps the decrease in the weight of the gonads of the experimental recipients is the result of decrease in either the follicle stimulating (Prolan A) or the luteinizing hormone (Prolan B). A histological study of ovaries of experimental recipients and control recipients does not show any qualitative differences, although the ovaries of the control recipients show more maturing follicles and corpora lutea than the ovaries of the experimental recipients. These observations are in accord with data obtained by weighing. We do not believe we can conclude anything from our data concerning the question of the duality of the gonad-stimulating hormones of the anterior pituitary or the influence of oestrin on them. The evidence indicates only that oestrin does decrease the resultant (size of the ovary) of the action of one or more hormones elaborated by the anterior pituitary.

Conclusions of similar nature can be drawn from the investigations concerning the influence of the oestrous hormone on the gonad of male and female animals, such as those of Kunde, D'Amour, Gustavson and

Carlson (1930) on female dogs; Golding and Ramirez (1928), Moore and Price (1930), Leonard, Meyer and Hisaw (1931), Wade and Doisy (1931) on rats; Haberlandt (1927) and Dahlberg and Akesson (1930) on mice. All of these investigators found that oestrin inhibited the normal development of the ovary or testis.

The inhibiting influence of oestrin on the male gonad led the earlier investigators to conclude that there is a gonadal hormone antagonism. Moore and Price (1930), Leonard, Meyer and Hisaw (1930) demonstrated that the development of the female as well as the male gonad is inhibited by the gonadal hormones of both sexes. The data presented in this report demonstrate by direct biological assay that the gonad-stimulating complex of the castrated male as well as the castrated female anterior pituitary is decreased by oestrin administration.

The conclusion is therefore apparent that the inhibiting influence of the gonadal hormones (male or female) on the gonad is mediated by way of the anterior pituitary and that a directly antagonistic action of the gonadal hormones on the gonad is not the more tenable explanation. This conclusion has also been expressed by Engle (1929b) and Moore and Price (1930).

The mechanism by which the oestrous hormone decreases the gonad-stimulating power of the anterior pituitary is not known but evidence concerning this mechanism is important in making any attempt to explain the cyclic rhythm of the female gonad. Two theories have been advanced to explain the rhythmical activity of the female gonad, both of which assume that oestrin is the substance which controls the gonad-stimulating complex. Engle (1931) first advanced the theory that oestrin causes a release of the stored complex; whereas Moore and Price (1930) presented evidence which led them to suggest that oestrin inhibits the production of the gonad-stimulating complex of the anterior pituitary. Later we (Leonard, Meyer and Hisaw, 1931) came to the same conclusion as Moore and Price from data obtained from a study of the effect of oestrin on the gonads and anterior pituitary of immature male and female rats.

The release mechanism theory assumes that the rhythmical increase and decrease in oestrin controls the rhythmical activity of the ovary. When the amount of oestrin is greatest the gonad-stimulating complex, stored during the period when the amount of oestrin is small, is released into the circulation. Probably a certain threshold amount of oestrin must be attained before the release of the hormone from the anterior pituitary is effected. It seems evident that this or any other theory must provide for the continuous production of small amounts of gonad-stimulating complex at all times regardless of the amount of oestrin being produced. That such a condition exists is evident from the growth of the immature ovary before puberty, at which time a small amount of oestrin is probably being produced. The evidence for the "release mechanism" theory has been discussed by Engle and is found in observations obtained by certain

indirect studies of the gonad-anterior pituitary interrelationship. The increase of the hormones in the anterior pituitary of castrated animals is one of the basic pieces of evidence for the "release mechanism" concept. This increase in gonad-stimulating power is thought to represent a storage of the hormone, an idea which is supported by the increase in the number of "castration cells" in the anterior pituitary after castration (Addison, 1917, and others). Further evidence for the theory advanced by Engle is found in the study on the gonad-stimulating power of the hypophysis of the guinea pig during oestrum and dioestrum (Smith and Engle, 1927b). They found that the gonad-stimulating power of the hypophyses of guinea pigs was greatest, as determined by implantation into immature mice, during the dioestrum. They were unable to obtain a satisfactory response in the test animals when the hypophyses of guinea pigs in oestrus were used. Recently Wolfe (1931) has studied the variation in amount of the gonad-stimulating complex in the hypophysis of the sow during the oestrous cycle. The quantitative test used was the minimum amount of the sow's hypophysis which was required to induce ovulation in the rabbit.

The results obtained by Wolfe demonstrated that the gonad-stimulating complex was to be found in the greatest amount when the sow was in prooestrous, in a smaller amount in oestrous, and least in dioestrous. Wolfe has suggested that these results may indicate that a large amount of oestrin may inhibit the production of the luteinizing hormone and that a small amount stimulate its production. It is also possible to explain the results obtained by Smith and Engle (1929) and Wolfe by the release mechanism theory, i.e., the gonad-stimulating complex increases in amount in the anterior pituitary of the guinea pig and sow during the dioestrum (attaining its maximum in the prooestrous phase of the cycle in the sow) and is released by the large amount of oestrin present at the time of oestrous.

The work of Evans and Swezy (1931) on ovogenesis in rat, dog, cat, monkey and man demonstrates that as the time of oestrus or ovulation approaches, the number of healthy growing follicles is the least as most of the follicles are undergoing atresia. However, at this time there are one or numerous Graafian follicles, depending on the species, which mature and ovulate. These facts are correlated with an increase in the amount of oestrin, as manifested in the reproductive tract of lower mammals and found in the blood and urine of human females (Siebke, 1931, and Frank, 1929). Thus it may be suggested on the basis of these observations that oestrin produces a release of stored gonad-stimulating complex which results in maturity and ovulation of the Graafian follicles.

The results of the investigations of Smith and Engle, Wolfe, and Evans and Swezy which have just been cited as supporting the "release mechanism" theory can also be used to support the theory which assumes that oestrin inhibits the production of the gonad-stimulating complex. The decrease in the amount of the gonad-stimulating complex found in the

guinea pig's and sow's hypophyses during oestrus may be the result of an inhibition of the production of the gonad-stimulating complex by oestrin. This interpretation would provide an explanation for the fact that follicular atresia is greatest at oestrus (Evans and Swezy). The decrease in the amount of oestrin which occurs after oestrus would allow for an increase in the production of gonad-stimulating complex in the anterior pituitary and thus provide the basis for an explanation of the large number of follicles and corpora lutea found in the ovary during the dioestrum. (The results obtained by Wolfe, 1931, from his study of the gonad-stimulating complex of the sow's hypophysis does not support this concept.) It must be admitted that the maturity of a few of the Graafian follicles at oestrus is difficult to explain on the basis of the "inhibition of production theory" unless it be assumed that there is a change in these few follicles which makes them sensitive to a small amount of the gonad-stimulating complex.

The results obtained by Philipp (1930), Ehrhardt and Mayes (1930) and Zondek (1931) demonstrate that the hypophyses of pregnant women contain very little, if any, gonad-stimuating complex. The large amount of oestrin which is produced in these women may be said to inhibit the production of the complex. This explanation assumes that oestrin and the gonad-stimulating substances found in the blood and urine of pregnant women are produced by the placenta.

Although it has been demonstrated by the specific data presented in this paper that oestrin decreases the amount of gonad-stimulating complex found in the anterior pituitary of castrated male and female rats, it is not known what influence oestrin has on the amount of the complex found in the blood. However, the work of Kallas (1930) seems to answer this question in a satisfactory way. He found that the injection of oestrin into the castrated immature female partner of parabiotic twin rats (the other twin being a non-castrated immature female) inhibited the precocious development of the immature female twin which would have resulted if oestrin had not been injected. He was unable to inhibit the precocious sexual maturity when the injected partner was a castrated male. [One of us (R.K.M.) in collaboration with Dr. Eduardo Bunster has corroborated the evidence presented by Kallas except for those observations which concern the injection of oestrin into the castrated male partner. We found that the result was the same whether the injected castrated partner was male or female.]

The results of the experiments on parabiotic rats demonstrate that the gonad-stimulating complex is not only increased in amount in the blood of castrated male and female rats, but also that oestrin is not necessary for the release of the complex but in reality inhibits its production by the anterior pituitary and thus produces a decreased amount in circulation.

It seems that practically all evidence available from investigations concerning the effect of oestrin on the gonads or anterior pituitary of animals supports the theory which states that oestrin inhibits the production of the gonad-stimulating complex. Evidence contrary to this view is to be found in the reports of Burch and Cunningham (1930) and Kraul (1931), who found that the potency of the anterior pituitary was increased by administration of the oestrous hormone. Burch and Cunningham arrived at their conclusions by finding an increase in the weight of the ovaries of the test animals (mice) and Kraul by an increase in the number of corpora lutea.

The evidence which we have obtained from injecting oestrin into castrated male and female rats could be the result of either a continuous release of the stored gonad-stimulating complex during the period of injection or the inhibition of production during the administration of oestrin. It seems probable that the final amount in the anterior pituitary would be decreased by whichever mechanism was operating. However, in view of the other evidence which we have cited in this discussion, we believe our data further support the theory that oestrin, in part at least, controls the rhythmical activity of the ovary by inhibiting the production of the gonad-stimulating complex of the anterior pituitary.

SUMMARY

Castrated male and female rats were injected with oestrin (Amniotin and Theelin) and their hypophyses removed and implanted into immature female rats. The ovaries of these immature recipients were weighed and compared with the ovaries of immature female rats which had received implants of the hypophyses of castrated male and female rats not injected with oestrin. It was found that the ovaries of those immature rats which received the hypophyses of the males injected with oestrin weighed 45 per cent less than the ovaries of the control recipients. The ovaries of the rats implanted with the hypophyses of castrated female rats injected with oestrin weighed 47 per cent less than those of the control animals. These facts show that oestrin decreases the amount of gonad-stimulating complex in the hypophyses of castrated male and female rats when compared with control animals. It is concluded that this decrease is a result of the inhibition of production of the gonad-stimulating complex by oestrin. The relationship of this conclusion and other data to two possible methods of explaining the rhythmical activity of the female gonad is discussed.

REFERENCES

Addison, W. F. H.: J. Comp. Neurol. **28**: 441. 1917.
Burch, J. C. and R. S. Cunningham: Proc. Soc. Exper. Biol. and Med. **27**: 331. 1930.
Dahlberg, G. and S. Akesson: Acta. obst. et gynec. Scandinav. **10**: 63. 1930.
Ehrhardt, K. and B. T. Mayes: Zentrabl. f. Gynäk. **54**: 2949. 1930.
Engle, E. T. Am. J. Physiol. **88**: 101. 1929a.
——: Am. J. Anat. **44**: 121. 1929b.
——: Endocrinology, **15**: 405. 1931.
Evans, H. M. and M. S. Simpson: Am. J. Physiol. **89**: 371. 1929.

Evans, H. M. and O. Swezy: Memoirs University Calif. **9**: 119. 1931.
Frank, R. T.: The Female Sex Hormone. Thomas, Springfield, Ill. 1929.
Golding, G. J. and F. T. Ramirez: Endocrinology, **12**: 804. 1928.
Haberlandt, L.: Arch. f. d. ges. Physiol. **216**: 325. 1927.
Kallas, H.: Klin. Wchnschr. **9**: 1345. 1930.
Kraul, L.: Am. J. Obst. and Gynec. **21**: 301. 1931.
Kunde, M. M., F. E. D'Amour, R. G. Gustavson and A. J. Carlson: Proc. Soc. Exper. Biol. and Med. **28**: 122. 1930.
Leonard, S. L., R. K. Meyer and F. L. Hisaw: Endocrinology, **15**: 17. 1931.
Meyer, R. K., S. L. Leonard, F. L. Hisaw and S. J. Martin: Proc. Soc. Exper. Biol. and Med. **27**: 702. 1930.
Moore, C. R. and D. Price: Proc. Soc. Exper. Biol. and Med. **28**: 38. 1930.
Phillip, E. 1930. Zentralbl. f. Gynäk. **54**: 450. 1930.
Smith, P. E. and E. T. Engle: Am. J. Anat. **40**: 159. 1927.
——: Anat. Rec. **42**: 38. 1929.
Siebke, N.: Archiv. f. Gynäk. **146**: 417. 1931.
Wade, N. J. and E. A. Doisy: Proc. Soc. Exper. Biol. and Med. **28**: 714. 1931.
Wolfe, J. M.: Am. J. Anat. **48**: 391. 1931.
Zondek, B.: Zentralbl. f. Gynäk. **54**: 450. 1931.
—— and S. Aschheim: Klin. Wchnschr. **6**: 248. 1927.

THE RELATION OF THE ADRENAL GLANDS TO THE RELATIVE ERYTHROCYTE VOLUME

EMMERICH VON HAAM, M.D.† AND HARVEY S. THATCHER, M.D.*

The mechanism of the fluctuations in the peripheric erythrocyte volume has been studied by a great number of authors during the past few years. Barcroft and others conclude that conditions which lead to contraction of the spleen produce an erythrocytosis in the peripheral blood. Benhamou, Jude and Marchioni consider this erythrocytosis a constant reaction of splenic contractions. Viale and Di Leo Lira, Crosetti, Binet, Abderhalden and Roske, Drastich and others confirm in animals that after the spleen is removed there is no reflex erythrocytosis in the peripheral circulation. Abderhalden and Roske, Scheunert and Krzywanek demonstrate that the splenic blood is more concentrated than the blood of the peripheral circulation. Mueller finds in the dog that the erythrocyte content of the splenic blood is 187.5 per cent compared to that of the blood in the peripheral circulation. He estimates the average storage volume of the spleen as 18.75 per cent of the entire lymphocytic content. Abderhalden and Roske calculate that the dilated spleen contains one-fifth of the total blood. Feldberg and Lewin find after partial asphyxiation of dogs that there is 20-30.5 per cent increase of the erythrocytes in the peripheral circulation. Benards, however, estimates from the work of Barcroft and Cruickshank, that there is only a possible increase of 1-2 per cent of the erythrocytes in the peripheral circulation after a maximum contraction of the spleen.

The mechanism which produces this erythrocytosis is complicated. Every contraction of the spleen is not followed by erythrocytosis. Radosavljevic and Sekulic emphasize that sodium nitrite produces a contraction of the spleen, causing a lowering of the blood pressure and a decrease of the erythrocytes in the peripheral circulation. Schiff believes that there are two different kinds of contractions of the spleen: (a) a "pale contraction," resulting from the contraction of the blood vessels and (b) a "red contraction," resulting from the contraction of the specific muscular system. Henschen and Huek describe a special opening and closing mechanism of the arterial system of the spleen comparable to sphincters, forming the anatomical basis for the function of this organ as a blood reservoir. Viale believes that contraction of the spleen is a physiological reflex and the spleen serves as a safety valve in regulating circulatory disturbances. Radosavljevic and Sekulic find that all drugs which cause a lowering of the blood pressure produce a contraction of the spleen, and all drugs which increase the blood pressure cause the spleen to dilate. Tour-

†Now Assistant Professor of Pathology at the Medical Center of the Louisiana State University, New Orleans, La.

*From the Department of Pathology, School of Medicine, University of Arkansas, Little Rock, Ark.

nade and Chabrol explain the paradoxic effect of adrenaline (contraction of the spleen with increase of blood pressure) as due to a nervous and a hormonal mechanism. Izquierdo and Cannon confirm the findings of the older literature that "brief asphyxia by mechanical obstruction of the air passage in normal animals is followed by erythrocytosis." They report that in animals with a denervated spleen, a higher effect of low oxygen tension on the red blood picture in the peripheral blood could be produced, as a rule, than in normal animals. This is explained by Izquierdo and Cannon as "extra adrenaline acting on the toneless spleen." Houssay and Molinelli find that the adrenaline secretion is increased after anoxaemia and this fact is responsible for the contraction of the denervated spleen. As proof for this opinion Izquierdo quotes only one animal which did not show the anoxaemic polyglobulia after removal of the medullary substance.

The purpose of the experiments herein reported is to study the relation of the adrenal glands on the relative erythrocyte volume, assuming that it is determined by contraction of the spleen.

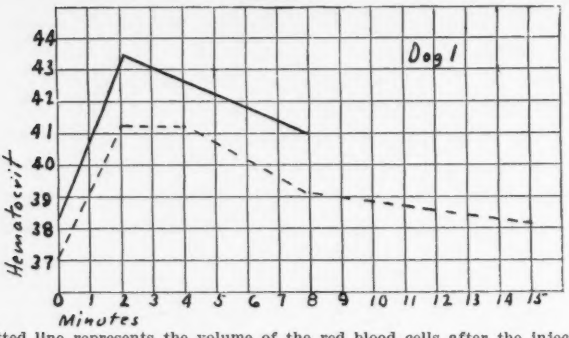
METHODS

The normal fluctuation of the peripheric blood volume of normal dogs was first determined by obtaining the increase of erythrocytes in the peripheral blood after adrenal injection, short asphyxiation and bleeding. This increase was determined by measuring the valume of red blood cells by means of the hematocrit (Starlinger). The blood was taken at 2, 4, 8, and 15-minute intervals. Each experiment required 15 to 20 cc. of blood. Morphine was first administered, followed by chloralose. Since chloralose lowers hematocrit readings, according to Abderhalden and Roske, and Isquierdo and Cannon, hematocrit levels established before the injection of the anesthetic were used as the basis of our calculations. Adrenaline was given in large doses in the femoral vein or mechanical obstruction of the upper air passage was produced by asphyxiation for short periods, or total bleeding was accomplished by opening the carotid artery. All three experiments lead to an extreme contraction of the spleen. This organ which becomes after chloralose injection, very large, decreases often to one-fourth or one-fifth of its size, the capsule becomes wrinkled and the organ becomes hard. This contraction of the spleen is accompanied by a more or less marked increase of the erythrocytes in the peripheric blood.

A typical example of the erythrocytosis in normal dogs after adrenal injection and mechanical obstruction of the air passage, illustrates that both curves are almost parallel (Chart 1).

After the determination of the limits of the contractility of the spleen, bilateral adrenalectomy was performed according to the method of Stewart and Rogoff. The operation was completed in two stages. The interval between the removal of the two glands was two to three weeks. Before the second adrenal was removed, hematocrit determinations similar to that performed on the normal animal were recorded. During the operation of

CHART 1.



The dotted line represents the volume of the red blood cells after the injection of adrenalin; the solid line represents the volume of the red blood cells after asphyxiation.

adrenalectomy, use was made of the retroperitoneal approach so that adhesions between the splenic capsule and the peritoneum could be prevented. Our dogs survived bilateral adrenalectomy for an average of six days, but the majority showed signs of adrenal insufficiency on the third day after operation. When the first signs of adrenal insufficiency appeared, further hematocrit determinations were made and the animal was bled by opening the carotid artery, shortly before its death. During the bleeding, several blood volume determinations were made and the curves compared with the hematocrit determinations obtained on five normal dogs. (See table IV.)

Twenty dogs were used, 11 of which survived the bilateral adrenalectomy long enough so that all three phases of the experiment could be completed. The other nine dogs died earlier. The results are shown in tables I to IV. The figures recording the percentage of the maximum increase of

TABLE I
NORMAL DOGS

Dog No.	Effect of Adrenaline Upon the Hematocrit Values of the Peripheric Blood		Effect of Asphyxia Upon the Hematocrit Values of the Peripheric Blood	
	Hematocrit Values Control	Per Cent of Maximum Increase	Hematocrit Values Control	Per Cent of Maximum Increase
1	37.0	14.1	38.3	13.3
2	40.0	16.0	40.0	5.5
3	36.0	22.4	39.2	15.8
4	38.8	19.1	38.8	14.4
5	34.2	36.5	32.2	24.8
6	41.2	20.4	40.6	28.5
7	40.4	35.2	43.1	10.2
8	33.2	15.1	31.1	25.7
9	44.0	0.7	40.2	9.9
10	35.6	24.4	34.1	26.3
11	40.1	19.9	40.1	29.9
12	32.1	27.0	33.0	27.8
13	41.1	7.3	37.6	15.4
14	39.2	0.0	39.1	2.5
15	36.0	14.4	35.6	16.0
16	35.6	11.2	35.4	16.3
17	41.3	10.4	40.1	18.9
18	40.5	1.7	37.1	13.7
19	37.0	8.6	36.8	8.9
20	37.7	11.6	35.4	18.1

The maximum increase of the hematocrit reading in normal dogs after contraction of the spleen.

the hematocrit value after contraction of the spleen are regardless of the elapsed time. We found, with few exceptions, that this highest difference occurred two minutes after the beginning of the experiments.

The hematocrit readings on our dogs at the beginning of the experiments fluctuate between 32.1 (dog 12) and 44.0 (dog 9). The average for 20 animals is 38.1. The fluctuations are not more than 15 per cent above or under this average. Chloralose caused a decreased volume of the red blood cells in the majority of our animals. This decrease, however, cannot be considered an absolute rule, since dogs 3, 5 and 7 do not show it and dogs 10 and 19 show even a slight increase. The greatest difference after chloralose is found in dog 4 with a decrease of 9.7 per cent. The cause of this diminution after chloralose (reported also by Izquierdo, and Abderhalden and Roske), might be in the dilation of the spleen. The organ is found swollen; its capsule is tight; and it has a deep bluish red appearance. The injection of adrenaline is followed in almost 100 per cent of our dogs by an increase of the volume of the red cells in the peripheral circulation. Only dogs 9 and 14 do not show this increase. The curves obtained by taking blood at certain intervals after the adrenaline administration show their maximum 4 minutes or sometimes 2 minutes after the injection of the drug. The greatest difference is reached in dog 5 with an increase of 36.5 per cent. The average increase after adrenaline injection in 20 dogs is 16.3 per cent. The fluctuation of the different figures is high and we have not been able to detect any rules as to sex or age in our animals. The increase of the volume of the erythrocytes obtained after a brief mechanical obstruction of the upper air passage (anoxaemic erythrocytosis) differs greatly in the various animals. The maximum increase is found in dog 11 with 29.9 per cent, a number which is nearly as high as that found by Feldberg and Lewin. A comparison of both groups of experiments shows that dog 14, which does not show any increase of erythrocytic volume in the peripheral circulation after adrenaline injection shows only a slight increase (2.5 per cent) after a short asphyxiation. Dog 9 also shows a slight increase in both experiments. The average increase in the second group is 17.1 per cent, which is very similar to the percentage obtained after adrenaline injection.

Table II sets forth the experimental data when one suprarenal gland has been removed by previous operation. The conditions of the experiments have been exactly the same and the tests were taken at a time when the operative wound was completely healed. The left adrenal was removed from dogs 1, 2, 4, 5, 6, 15, 17, 18, and 20; the right, from dogs 4, 8, 10, 11, 12, 13. Dogs 3, 7, 14, 9 and 19 died during or shortly after the operation.

The removal of one adrenal gland has no effect or only a slight effect on the contractility of the spleen. The average increase of the hematocrit readings is 13.1 per cent in our 15 dogs. The maximum increase is found in dog 6 with 20.5 per cent; the minimum, in dog 10 with 5.7 per cent. The

TABLE II

UNILATERALLY ADRENALECTOMIZED DOGS

Dog No.	Effect of Adrenaline Upon the Hematocrit Values of the Peripheric Blood		Effect of Asphyxia Upon the Hematocrit Values of the Peripheric Blood	
	Hematocrit Values Control	Per Cent of Maximum Increase	Hematocrit Values Control	Per Cent of Maximum Increase
1	36.0	13.3	37.1	8.3
2	38.0	15.7	40.8	10.7
4	36.2	11.5	37.2	11.0
5	35.1	15.6	35.1	11.6
6	40.0	20.5	40.1	26.4
8	34.1	14.8	32.1	0.3
10	34.1	5.8	36.1	9.9
11	38.1	18.3	36.1	30.4
12	34.0	13.2	35.0	6.2
13	40.0	12.8	38.0	20.9
15	38.2	4.4	35.1	14.8
16	37.3	16.3	35.1	14.8
17	39.5	10.1	36.1	9.1
18	40.0	14.0	39.2	10.9
20	38.0	10.4	38.4	18.7

Maximum increase of erythrocytic volume in unilateral adrenalectomized dogs after contraction of the spleen.

course of the hematocrit curves is unchanged and the highest point is reached 2 to 4 minutes after the injection of the drug. This is similar to the findings in normal dogs. The anoxaemic erythrocytosis caused by reflex contraction of the spleen after a short mechanical obstruction of the air passage shows an average of plus 13.6 per cent with a maximum of 30.4 per cent in dog 11, and a minimum of 0.3 per cent in dog 8. The highest point of the hematocrit curve is reached 2 minutes after the short asphyxiation. The data of this series show a high variation in the individual animals. There is no difference between the animals whose right adrenal gland has been removed compared with those whose left adrenal gland has been extirpated. Both series show the same average increase (13.1 per cent and 17.1 per cent), which corresponds to our findings in normal dogs (16.3 per cent and 17.1 per cent).

Table III shows the variation of hematocrit readings on the peripheral blood in dogs after bilateral adrenalectomy. Of the 15 dogs which sur-

TABLE III

BILATERALLY ADRENALECTOMIZED DOGS

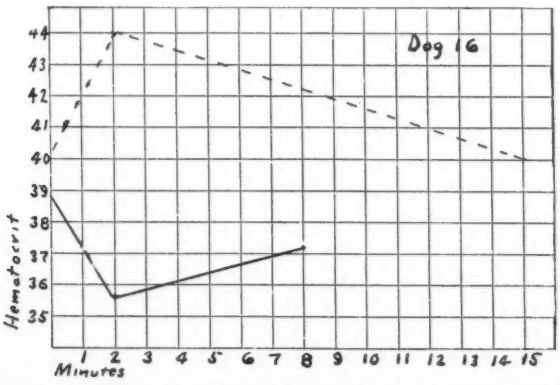
Dog No.	Effect of Adrenaline Upon the Hematocrit Values of the Peripheric Blood		Effect of Asphyxia Upon the Hematocrit Values of the Peripheric Blood	
	Hematocrit Values Control	Per Cent of Maximum Increase	Hematocrit Values Control	Per Cent of Maximum Increase
1	34.1	14.9	36.1	2.7
5	29.2	....	29.2	4.7
6	36.1	14.1	35.8	9.5
8	38.3	8.1	....	....
11	40.3	10.4	39.9	2.7
12	37.3	....	37.3	4.5
13	31.6	9.5	31.1	5.4
16	40.1	9.7	38.9	9.2
17	43.6	....	43.6	8.0
18	34.6	11.8	34.1	2.3
20	29.5	13.2	28.8	4.8

Maximum increase of hematocrit determinations on bilaterally adrenalectomized dogs after contraction of the spleen.

vived the first operation, only 11 could be used for these tests. Dogs 2, 4, 10 and 15 died so soon after the removal of the second gland that a test could not be made. From dogs 1, 5, 6, 17, 18, and 20 the remaining right adrenal was extirpated in the second operation; from dogs 8, 11, 12, 13 and 16, the remaining left adrenal was extirpated in the second operation. In some of our bilateral adrenalectomized dogs symptoms of adrenal insufficiency at the time the tests were performed were so marked that it was not deemed advisable to take a great amount of blood. On these dogs, only one test was performed. On dogs 1, 6, 11, 13, 18 and 20, both tests could be made similar to those in the previous series. On dog 8, only the adrenalin test was made. On dogs 5, 12, and 17 only the test of anoxaemic erythrocytosis was performed. On dog 20, the final blood test after adrenaline injection was omitted. On dog 1, the final blood test after asphyxiation was omitted.

The average increase of the volume of the red blood corpuscles of the peripheral blood after the injection of adrenaline in adrenalectomized dogs is 11.4 per cent; the maximal increase, 14.1 per cent (dog 6); the minimal increase, 8.1 per cent (dog 8). The course of the curve is unchanged. The fluctuation in the various animals is smaller than in the previous series, but the number of the animals is also considerably smaller. In the majority of our cases a decrease in the hematocrit readings on the peripheral blood after a short mechanical obstruction of the air passage is found. The determination of the average change of the hematocrit findings gives a decrease of 2.3 per cent; the maximum in dog 5 (4.7 per cent); the minimum in dog 16 (9.2 per cent). In ten animals, four show an increase and six a decrease of erythrocytic volume. The curves are irregular, sometimes showing a slight increase in volume at the beginning and a decrease at the conclusion of the experiment (dog 5). Some of the changes are

CHART 2.



The dotted line represents the volume of the red blood cells after the injection of adrenalin in adrenalectomized dog; the bold line represents the volume of the red blood cells after asphyxiation.

found 2 minutes and other 8 minutes after the beginning of the experiment. Therefore, differences can be observed in the course of the hematocrit curve after the injection of adrenaline and after a short asphyxiation of the adrenalectomized dogs. (See chart II.)

The parallelism between the adrenaline erythrocytosis and anoxaemic erythrocytosis (Chart 1), is therefore completely changed.

In order to determine the influence of the adrenal glands on the contraction of the spleen caused by acute anemia, the adrenalectomized animals have been bled to death by opening the carotid artery. During the bleeding samples of blood have been taken and erythrocytic volume determined. The "bleeding curve" of the adrenalectomized animals has been compared with the "bleeding curve" of normal dogs. The results of this series of experiments are shown in table IV.

TABLE IV

BILATERALLY ADRENALECTOMIZED AND NORMAL DOGS

Bilaterally Adrenalectomized Dogs			Normal Dogs		
Dog No.	Hematocrit Values Control	Per Cent of Maximum Increase During Bleeding	Dog No.	Hematocrit Values Control	Per Cent of Maximum Increase During Bleeding
1	37.2	0.	24	36.2	3.8
5	28.6	0.	25	42.8	5 6
6	36 6	1.1	26	38.9	7.9
8	36.4	0.0	27	37.7	0.
11	41.1	0.	28	39.1	1.7
12	36.5	2.7			
13	29.6	0.			
17	40.1	1.2			
18	34.3	0.			
20	27.1	0.			

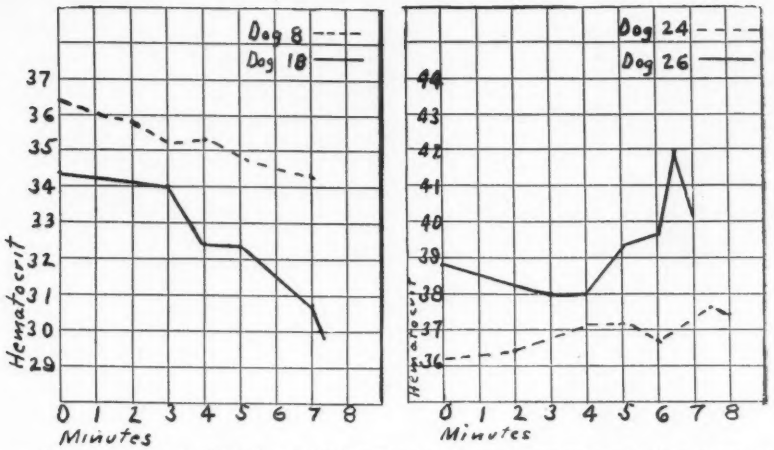
Effect of bleeding on bilaterally adrenalectomized and normal dogs.

The average increase of the hematocrit determination of adrenalectomized animals when bled to death is 0.5 per cent. Three of 10 animals show this slight increase. The maximum is in dog 12 with an increase of 2.7 per cent. The majority of adrenalectomized dogs show a distinct decrease of the hematocrit of the peripheral blood toward the end of the bleeding (dogs 1, 5, 6, 8, 11, 12, 13, 18 and 20). The decrease can be high as (in dog 13) 14.9 per cent. The average increase of the hematocrit determinations of normal dogs when bled to death is 3.5 per cent. Four of five dogs show a distinct increase before death. This increase is 7.9 per cent in dog 26. This difference is illustrated in the curve (Chart 3).

Table V represents the average results of our experiments.

The decrease in the hematocrit values of adrenalectomized dogs can be explained by the loss of blood in the operation. Our animals have not been observed a sufficient length of time after the second operation to show the polycythaemia as found by other authors in animals three days or longer after the adrenalectomy. The average increase of erythrocytes in the peripheric blood after asphyxia and bleeding is markedly less than after

CHART 3.



The two curves at the left are the hematocrits of the adrenalectomized dogs 8 and 18. The two curves at the right are the hematocrits of normal dogs 24 and 26, during the bleeding process.

the injection of adrenaline in animals without adrenal glands. This is in distinct contrast to normal animals or animals whose one adrenal gland has been removed.

TABLE V

Group of Animals	Average of Hematocrit Values at Beginning of the Experiment	Average of Increase of Hematocrit Values in Per Cent		
		After Adrenaline	After Asphyxia	After Bleeding
Normal dogs.....	37.1	15.8	17.1	3.8
Dogs with one adrenal gland removed.....	37.2	13.11	13.6	....
Dogs with both adrenal glands removed.....	35.5	11.9	2.5	0.5

SUMMARY

1. The intravenous administration of adrenaline, asphyxia and bleeding produced a short lasting increase of the erythrocytes in the peripheral blood of 20 dogs. The autopsy revealed in all cases a marked contraction of the spleen during the time the hematocrit values in the peripheral blood were increased.

2. Adrenalectomy prevented or hindered the reflex which leads to the splenic contraction and to the acute erythrocytosis in the peripheral blood after asphyxia and bleeding.

3. It is concluded that the adrenal glands or their secretion, adenaline, play an important part in the reflex mechanism which regulates the distribution of erythrocytes in the body.

REFERENCES

1. Abderhalden, E. and G. Roske: Arch. f. d. ges. Physiol. **216**: 308. 1927.
2. Barcroft, J.: Ergebn. d. Physiol. **25**: 818. 1926.
3. Benard, R., quoted by A. Radosavljevic and M. Sekulic: Wien. Arch. f. inn. Med. **20**: 81. 1930.
4. Benhamou, E., Jude and R. Marchioni: Compt. rend. Soc. de biol. **100**: 456. 1929.
5. Binet, L.: La Physiologie de la Rate, Paris. 1927.
6. Crosetti, L.: Arch. Sci. Med. **52**: 625. 1928.
7. Cruickshank, E. W. H.: J. Physiol. **61**: 455. 1926.
8. Drastich, L.: Arch. f. d. ges. Physiol. **217**: 598. 1927.
9. Feldberg, W. and H. Lewin: Arch. f. d. ges. Physiol. **219**: 246. 1928.
10. Henschen, C. and H. Reissinger: Deutsche Ztschr. f. Chir. **210**: 1. 1928.
11. Houssay, B. A. and E. A. Molinelli: Am. J. Physiol. **76**: 538. 1926.
12. Hueck, W.: Verhandl. d. deutsche. Ges. f. inn. Med., Kongr. **40**: 472. 1928.
13. Izquierdo, J. J. and W. B. Cannon: Am. J. Physiol. **84**: 545. 1928.
14. Izquierdo, J. J.: Am. J. Physiol. **86**: 145. 1928.
15. Mueller, H. K., quoted by A. Radosavljevic and M. Sekulic: Wien. Arch. f. inn. Med. **20**: 81. 1930.
16. Radosavljevic, A. and M. Sekulic: Wien. Arch. f. inn. Med. **20**: 81. 1930.
17. Scheunert, A. and F. W. Krzywanek: Arch. f. d. ges. Physiol. **217**: 261. 1927.
18. Schiff, P., quoted by A. Radosavljevic and M. Sekulic: Wien. Arch. f. inn. Med. **20**: 81. 1930.
19. Stewart, G. N.: Endocrinology, **5**: 283. 1921.
20. Tournade, A. and M. Chabrol: Compt, rend. Soc. de biol. **90**: 835. 1924.
21. Viale, G.: Compt. rend. Soc. de biol., **99**: 2008. 1929.
22. Viale, G. and J. Di Leo Lira: Comp. rend. Soc. de Biol. **96**: 229. 1927.

ABSTRACTS

Appearance of a medullary reaction in the cortical substance of an abscessed adrenal (Inversion réactionnelle de la substance corticale et de la substance médullaire, dans les capsules surrénales abcédées). Abelous, J. E. and R. Argaud, Compt. rend. Soc. de biol. **102:** 893. 1929.

In the adrenal of a sheep, the medulla was replaced by a mass of necrotic material. The cortex, however, gave the chomaffin reaction and Vaulpian's reaction with perchloride of iron.—J. C. D.

Etiology and clinical aspects of acute suprarenal insufficiency (Hemorrhages and hypoplasia of suprarenals) (Zur Ätiologie und Klinik der akuten Nebenniereninsuffizienz [Nebennierenblutungen und Hypoplasie]). Baumann, T., Ztschr. f. Kinderh. **51:** 276. 1931.

The various theories of suprarenal insufficiency in the newborn and infant and their extensive literature are discussed. A description of the typical picture of acute suprarenal insufficiency is given, such as it occurs particularly in hemorrhage of the suprarenals. The syndrome is characterized by high and often excessive temperature and very rapid respiration. The onset is sudden and usually suggestive of pneumonia. Cyanosis and petechiae are common and quite characteristic. Death occurs mostly within the first 24 hours. There is a good clinical description of two such cases, showing the typical syndrome, while autopsy revealed hemorrhagic destruction of both suprarenals. The author reports also a fatal case of bronchopneumonia in which the pulmonary lesion was limited in extent. The symptoms are somewhat similar to those in the previously described cases, but the course of the disease was prolonged. At autopsy hypoplasia of both suprarenals was found. The most common cause of acute suprarenal insufficiency is infection. All three cases described belong to the infectious group.—M. A. Goldzieher.

The increase of amino acids in the blood after adrenalin in normal individuals (L'aminoacidémie adrénalinique chez l'homme normal). Benhamou, E. and R. Gille, Compt. rend. Soc. de biol. **107:** 173. 1931.

After the subcutaneous injection of 1 mgm. of adrenalin chlorhydrate, there was regularly a rise in amino acid in the cases tried. In three splenectomized individuals this rise was absent. The increase is the result of the contraction of the spleen induced by adrenin.—J. C. D.

Effect of radiation in a case of pseudohermaphroditism with malignant adrenal cortical tumor (Uber der Erfolg der Roentgenbestrahlung in einem Falle von Pseudohermaphroditismus mit malignen Nebennierenrindentumoren). Gold, E., Arch. f. klin. Chir. **158:** 500. 1930.

This is a very interesting report of an individual reared as a girl until the age of 13 years and who presented the general appearance of that sex. The external genitalia showed a condition of pseudohermaphroditism with a 4 cm. penis-like structure, female labial formation and small introitus. Exploratory operation was performed for a tumor over the symphysis and another in the left splenic region. Because of inability to determine the sex, no biopsy was performed and radiation treatment was considered. Nine radiations were given over a period of two years over the site of the tumors. There was a change in the patient to male characteristics, both physically and psychologically. There were definite emissions and ejaculations. The tumors had entirely disappeared. The author considers the case to have been one of masculine pseudohermaphroditism due to adrenal tumor.—M. B. G.

Metabolic studies in Addison's disease: The effect of treatment with the cortical hormone of the suprarenal gland. Greene, C. H., L. G. Rowntree, W. W. Swingle and J. J. Pfiffner, Am. J. M. Sc. **183:** 1. 1932.

A study has been made of the chemical and metabolic changes observed in cases of Addison's disease, and the effect on these changes of treatment with the cortical hormone of the suprarenal gland. It is emphasized that the clin-

ical course of a case of Addison's disease may arbitrarily be divided into three stages: (1) The stage of initial destruction of the suprarenal glands; (2) the stage of the recognizable clinical syndrome, and (3) the terminal stage or crisis. Usually the disease is not recognized until the second stage is reached. At this time there may be loss of weight, asthenia and definite undernutrition. The basal metabolic rate is reduced slightly and there is some reduction in the blood sugar. Such changes become less with treatment, and more marked in the periods of crisis. The quantities of the various constituents of the urine in Addison's disease corresponded to the lower levels of the usually accepted normal standards. Creatinuria was present in a considerable proportion of cases. Retention of practically all urinary constituents was noted in one case in the course of a period of diminished urinary output. The nitrogen balance of those patients who were losing weight was negative. The majority of patients gained weight as a result of treatment with the suprarenal cortical hormone. In such cases the nitrogen balance became markedly positive. The period of crisis was characterized by gastrointestinal upsets, nausea and vomiting, pains, circulatory collapse, low blood pressure, dehydration and renal insufficiency. The effect of the last two dominated the chemical picture at this time. The relation between the chemical and metabolic changes observed in cases of Addison's disease, and those reported in suprarenalectomized animals, and the use of these changes for the standardization of preparations of the suprarenal cortical hormone are considered.

—Authors' Summary.

Growth of tumors in decapsulated white rats (La croissance des tumeurs chez les rats blancs privés de capsules surrénales). Laclau, N. C., Compt. rend. Soc. de biol. **106:** 146. 1931.

Sixty-five rats were implanted with carcinoma or fusiform cell sarcoma. These were decapsulated and the growth of the tumor tissue compared with that on suitable controls. The decapsulated animals died very rapidly from the effects of the cancer but the tumor growth was the same in decapsulated and control animals.—J. C. D.

The distribution of lipoidal phosphorous in the adrenal glands of certain mammals (Sur la répartition du phosphore lipidique dans les glandes surrénales de quelques mammifères). Leulier, A. and L. Revol, Compt. rend. Soc. de biol. **106:** 667. 1931.

The cortex and medulla of the sheep, cow, pig, horse, bull calf, female goat, and mule were examined separately. The cortex contained only about 25% more lipoidal phosphorous than the medulla.—J. C. D.

Effect of adrenin and acetylcholine on the pressure of the spinal fluid (Action de l'adrénaline et de l'acétylcholine sur la pression rachidienne).

Variations of spinal fluid pressure and venous pressure as influenced by adrenin (Les variations respectives de la pression rachidienne et de la pression venieuse sous l'influence de l'adrénaline). Loeper, M., A. Lemaire and J. Patel, Compt. rend Soc. de biol. **102:** 810; 812. 1929.

In dogs, adrenin produces a rise equal and parallel to that of the blood pressure in the carotid artery and external jugular vein.—J. C. D.

Golgi apparatus and vacuoles in the adrenal of pregnant guinea pigs (Appareil de Golgi et vacuome dans la surrénale de cobaye gravide). Merland, P. A., Compt. rend. Soc. de biol. **102:** 919. 1929.

A cytological study: In the cortex there are spherical vacuoles. These are small in the glomerulosa and large in the fasciculata. With these is associated the Golgi net.—J. C. D.

Glycemia in relation to x-ray irradiation of the adrenal (La glycémie dans l'irradiation surrénale). Molfino, F., Rev. franç. d'endocrinol. **8:** 325. 1930.

Treatment seems to produce two types of results dependent upon the endocrine condition of the patient; in sympathetic tonus the tendency is to increase glycemia; in vagus tonus the increase is slight or negligible. Explanation of the results is based on a neuro-vegetative foundation, or on a different susceptibility of the adrenal to the rays in the two types of individuals.—B. C.

Phosphorous content in the brain and spinal cord of animals after repeated injections of adrenin (Teneur en phosphore du cerveaus et du cervelet chez les animaux ayant recu des injections répétées d'adrénaline). Parhon, C. I. and G. Werner, Compt. rend. Soc. de biol. **105:** 73. 1930.

Seven to 15 daily doses of 0.3 mgm. to 0.5 mgm. of adrenin hypodermically were followed in rabbits by a reduction of phosphorous in the brain and spinal cord.—J. C. D.

Action of adrenin on local immunization with staphylcoccus antivirus (Action de l'adrénaline sur l'immunisation locale par l'antivirus staphylococcique). Poleff, L., Compt. rend. Soc. de biol. **106:** 431. 1931.

A few drops of adrenin injected into the conjunctiva of rabbits at the same time as the antivirus re-enforces its protective action.—J. C. D.

Some chemical effects from constant intravenous epinephrine injection in dogs. Samson, P. C. and H. R. D. Jacobs, Am. J. Physiol. **99:** 433. 1932.

Epinephrine was administered intravenously to unanesthetized dogs at constant rates over relatively long periods of time (up to 13 days). Continuous epinephrine administration resulted in a transient hyperglycemia and glycosuria, both of which disappeared in 24 hours. The normal glycemia persisted with continued injection, even when the rate of administration was doubled, and there was no further glycosuria. The cessation of epinephrine administration while the blood sugar values were within normal limits, led to an abrupt hypoglycemia with a slower return of the blood sugar to normal values. With further injection a second hyperglycemia and glycosuria occurred, although not as marked as the first. Continuous epinephrine administration increased the urinary output in every case. Continuous epinephrine injection did not affect the urinary nitrogen excretion as measured by twenty-four-hour periods.—Authors' Summary.

The properties of the adrenal lipoids (Sur les propriétés du lipoide surrénal). Steel, J., Compt. rend. Soc. de biol. **106:** 406. 1931.

The adrenal lipoids when mixed with oxidized adrenin seem to have the power of reducing it and resynthesizing active adrenin. It is suggested that this reactivation of adrenin may be a function of the cortex.—J. C. D.

Curare and secretion of adrenin (Curare et adrenalino-secretion). Tournade, A., H. Hermann and F. Jourdan, Compt. rend. Soc. de biol. **106:** 341. 1931.

Two dogs were joined by an anastomosis of the jugular vein of dog A with the adrenal vein of dog B. Dog A was decapsulated. Curare administered to dog B did not decrease adrenin secretion for more than two or three minutes as shown by the response of dog A. It did render dog B incapable of showing any response to adrenin because it paralyzed the vasomotor system. —J. C. D.

The central action of adrenin (Sur l'action centrale de l'adrénaline). Tournade, A., Compt. rend. Soc. de biol. **106:** 442. 1931.

If the renal vein and artery of dog A are joined to the jugular and carotid of dog B and adrenin injected into A, the resulting constriction of the kidney must be due to the action of the vasoconstrictor nerves since the kidney is isolated from the circulation of dog A. These have been stimulated by the action of the adrenin on the vasomotor center. Occasionally, there is vasodilitation. This is due to the direct action of adrenin in the blood which reaches the kidney from the circulation of dog A by way of aberrant vessels.—J. C. D.

The effect of adrenalin on the blood pressure of the elasmobranch, Squalus acanthias. Wyman, L. C. and R. Lutz, Biol. Bull. **62:** 17. 1932.

Intravenous injection of adrenalin, in doses as low as 2 cc. of 1:500,000, produced long-sustained pressor effects in Squalus acanthias, together with marked increase of pulse pressure and a tendency toward decrease of heart rate. Subsequent doses of adrenalin following doses stronger than 1:500,000 were ineffective. This is interpreted as being due to already existing maximum pressor action. Doses subsequent to a dose of 2 cc. of 1:500,000 were effec-

tive. The pressor effect is interpreted as being due to extra-cardiac factors, peripheral to the gill capillaries, but the region of action of the adrenalin was not located.—Authors' Summary.

Cutaneous diseases from the metabolic and endocrine aspect. Busman, G. J., Pennsylvania M. J. **35**: 172. 1931.

Cutaneous lesions may or may not be pathognomonic of general conditions. We know nothing about the internal pathogenic mechanism even in those dermatoses in which endocrine etiology is assured. A diabetic tendency is often associated with pruritus, carbuncle, furuncle, follicilitis, xanthoma and gangrene. Improper fat metabolism is often apparently responsible for eczema in infants, acne, seborrhea and psoriasis. Many cutaneous conditions such as eczema, pruritus, allergic dermatoses and psoriasis have been ascribed to protein hypersensitivity or toxic effects of its end products. Among the dermatological conditions of known endocrine causation are the pigmentation of skin and mucous membranes in Addison's disease, vitiligo and alopecia in hyperthyroidism, angioneurotic edema in Graves' disease, and scleroderma in multiglandular dysfunction.—I. B.

Pancreatic diabetes and the pituitary in the dog (Pankreasdiabetes und Hypophyse beim Hund). Houssay, B. A. and A. Biasotti, Pflüger's Arch. f. d. ges. Physiol. **227**: 664. 1931. Abst., Physiol. Absts. **16**: 622.

The removal of the pituitary in pancreatectomized dogs decreases the severity of the diabetes. The animals can survive without insulin for periods up to 6 months; there is usually loss of weight, but transitory rises in weight are occasionally observed. Pancreatic diabetes develops sometimes very slowly in hypophysectomized animals. The blood sugar is nearly always lower than in ordinary experimental pancreatic diabetes. Hypoglycaemic convulsions may be observed in pancreatectomized, hypophysectomized animals, and are often fatal; occasionally death can be prevented by the repeated injection of sugar. The glycosuria in these animals is, as a rule, less marked. The excretion of sugar decreases or ceases completely in the fasting animal. After the administration of sugar, the diabetes becomes more severe; only part of the sugar is excreted and the respiratory quotient rises. Destruction of the tuber or of the corpora mammilaria has no effect on the course of pancreatic diabetes. Marked degenerative changes in the parathyroid glands were observed in hypophysectomized, pancreatectomized animals.

Importance of sympathetic system in metabolism (Importance du systeme vegetaif sur le metabolisme). Laschke, E., Presse méd. **39**: 1517. 1931. Abst., J. A. M. A. **97**: 1745.

Leschke discusses the various hypotheses on the etiology of diabetes insipidus, sugar diabetes, and disorders in fat metabolism. His observations are contrary to the theory that the hypophysis is the etiologic factor in diabetes insipidus. Hypophyseal alterations when present are secondary factors to the rôle of the thalamencephalon, which acts through the central sympathetic nervous system in the regulation of water-mineral metabolism. The endocrine factor in pancreatic diabetes is given second place to the sympathetic nervous system, since the production of insulin itself is regulated by the sympathetic system. His observations prove that pancreatic diabetes does not depend on the amount of insulin secreted or parallel the changes in the islands of Langerhans. The assertion is made that polyuria is almost always a sign of disorder in the pluri-sympathetic regulation of water and mineral metabolism. Constant chloride retention in diabetes is an indication of aggravation of the conditions in metabolism; and a sudden diminution of chlorides is a forewarning of coma. There is also a relationship between arterial pressure and diabetes. Idiopathic hypertonia may cause the appearance of sugar in the blood and alimentary glycosuria. The author breaks down the old theories that named the hypophysis as chief cause and substitutes the diencephalon as a factor in adiposogenital dystrophies as well as obesity in general. Endogenous obesity is designated in this classification as a symptom of vagotonia. The author designates as plurisympathetic many regulatory disorders of the diencephalon in which diabetes insipidus may be combined with disorders in sugar metabolism regulation of temperature, obesity, hypertonia and polyuria, as well as regulation of the basic instincts.

Studies on conditions of activity in endocrine organs. XXVIII. Some effects of sympathin on the nictitating membrane. Rosenblueth, A. and W. B. Cannon, Am. J. Physiol. **99**: 398. 1932.

A method is described by which the smooth muscle in the nictitating membrane, sensitized by being previously disconnected from the superior cervical ganglion and by action of cocaine, can be used to record the presence of adrenin and sympathin in the circulating blood. The membrane can be used as a quantitative indicator "Dial" as an anesthetic does not interfere with the action of adrenin and sympathin on the nictitating membrane. Sympathin is produced when occasionally contracted smooth muscle (e.g., of the hairs), and also when tonically contracted smooth muscle (e.g., of the blood vessels), are stimulated by sympathetic impulses. The amount of sympathin produced on stimulation of smooth muscle, when circumstances are comparable, depends on the size of the area stimulated. Sympathin and adrenin liberated into the circulation at the same time act coöperatively. The liver discharges into the circulating blood a substance which acts like sympathin. The relation between this substance and the hepatic cardio-accelerator agent described by Cannon and Uridil (1921), and the question of its identity with sympathin, are considered.—Authors' Summary.

The roentgenographic treatment of feeble-mindedness in children (Über die Strahlenbehandlung des kindlichen Schwachsinnes). Weser, W., Jahrb. f. Kinderh. **134**: 120. 1931.

Weser gives a résumé of his well-known treatment of feeble-mindedness in children by means of the x-ray. He states that good results have been obtained by him in mental retardation due to traumatic, inflammatory or degenerative processes and also those due to endocrinopathies, whether primary or secondary.—M. B. G.

Influence of ischemia on the evolution of the elements in the mammalian testis. Transformation of Sertoli cells into cells of the interstitial type (Influence de l'ischémie sur l'évolution des éléments du testicule des mammifères. Transformations des cellules de Sertoli en cellules de type interstitiel). Aron, E., Compt. rend. Soc. de biol. **102**: 1062. 1929.

The principal artery of the testes was ligated in guinea pigs and rabbits. Under the conditions of reduced circulation which followed, the reproductive cells disappeared and the Sertoli cells changed into interstitial cells—J. C. D.

Transplantation of a teratomatous ovarian tumour in the fowl: Production of a sex hormone by the cells of the transplants. Baker, S. L., Lancet, **1**: 742. 1931.

Portions of a teratomatous ovarian tumour from a white leghorn pullet were successfully transplanted into 4 to 6 weeks old white leghorn chicks. The author describes his results as follows: The predominating cells in the original tumour and in the transplants resembled those in the theca interna of the ovarian follicles, lipoid-containing cells being a prominent feature. In addition, there were sparsely scattered groups of columnar celled tubules and keratinising epithelial masses. The original tumour-bearing fowl showed a fully developed oviduct but an undeveloped immature ovary. Young birds bearing tumour transplants showed a precocious development of the oviduct, the cloacal orifice of which became perforate. The ovaries of these birds remained immature.—L. B. Nice.

A comparative study of the Aschheim-Zondek and Mazer-Hoffman tests for early pregnancy. Bland, P. B., A. First and P. Roeder, Am. J. Obst. & Gynec. **23**: 83. 1932.

The present report is based upon a study of 248 patients, of whom 35 were controls, in whom the diagnosis was definitely known, 200 were problem cases, and 13 involved the question of life or death of the ovum. It appeared that the anterior pituitary hormone test of Aschheim and Zondek is a reliable laboratory adjuvant for the diagnosis of early pregnancy. In our hands it yielded 82.4% correct positives and 93.2% correct negatives. The finding of 6.8% false positive results, detracts, somewhat, from its complete reliability.

Especially is this error likely to be encountered in women who are functionally sterile, due to endocrine disturbances, or in women approaching the menopause. In these women, a compensatory hypertrophy of the anterior hypophysis may produce an excessive quantity of hormone, which, finding its way into the urine, will render an incorrect positive. The female sex hormone test of Mazer-Hoffman yields a smaller percentage of correct positives (76.3%) but is somewhat more reliable in the positive diagnosis of pregnancy, especially in patients suffering with functional disturbances. A smaller percentage of false positives, among non-pregnant patients (none in our series), was observed when this test was employed. This is probably due to the fact that hyperfunction of the ovaries, which would be necessary in order to produce an excess of female sex hormone in the urine, and render a false positive, is rarely, if ever, found in cases of endocrine dysfunction. In those patients in whom there is a question of a dead fetus (missed abortion), the presence of a positive Aschheim-Zondek and a negative Mazer-Hoffman test, on repeated occasions, denotes that the fetus is probably dead. It appears that the female sex hormone disappears from the urine somewhat earlier than does the anterior pituitary hormone. Repeated negative Mazer-Hoffman tests in pregnancy in those cases accompanied by slight bleeding, denotes an insufficient quantity of female sex hormone, and a threatened abortion. Only when the female sex hormones appear in demonstrable quantities in the urine, may one feel assured that the ovum has secured a firm location, and that the pregnancy may continue. The larger percentage of correct positives with the Aschheim-Zondek test, and the smaller percentage of false positives with the Mazer-Hoffman test, suggests that both tests be simultaneously employed in every instance in order to yield the most accurate results.—Authors' Summary.

Effect of injections of urine from pregnant women on immature, castrated and irradiated male rats (L'action des injections d'urine de femme gravide chez le rat male impubère, chatré ou irradié). Bourg, R., Compt. rend. Soc. de biol. **104**: 1046. 1930.

Daily injections of 1 cc. of urine were given for 5 to 10 days. Rapid hypertrophy of the testes and the genital tract resulted in the normal immature animals. This was lacking in the castrates. Irradiated animals showed degeneration of the reproductive epithelium but uninjured interstitial tissue. In these rats treatment with the urine resulted in marked hypertrophy of the testes and genital tract. The interstitial cells are, therefore, essential for the action of the hormone present in the urine of pregnant women.—J. C. D.

Comparative studies of prolonged injections of urine from pregnant women in irradiated and non-irradiated young male rats (Etude comparée des injections prolongées d'urine de femme enceinte chez le rat impubère male irradie et non irradié). Bourg, R., Compt. rend. Soc. de biol. **106**: 44. 1931.

Repeated injections of urine from pregnant women gives a precocious development in the genital tracts of young male rats. Both the germinal epithelium and the interstitial tissue take part. If rats are properly irradiated the germinal epithelium is destroyed but the interstitial tissue is left intact. Such animals when injected show a rapid development of the genital tract similar to that of the non-irradiated animals. This development, however, is not as complete.—J. C. D.

Inhibition by heifer serum of the appearance of neutral characters in ovariectomized chickens (Inhibition, par le sérum de Génisse, des caractères de neutralité chez les poules ovariotomisees). Busquet, H., Compt. rend. Soc. de biol. **106**: 633. 1931.

The serum when administered daily by mouth to ovariectomized pullets preserved their female characteristics. In castrated cocks regression to the neutral type took place in spite of serum feeding.—J. C. D.

Chemical investigation of the sex hormone (Über die chemische Untersuchungen der Sexualhormone). Butenandt, A., Ztschr. f. angew. Chem. **44**: 905. 1931.

The author assigns the empirical formula of $C_{18}H_{22}O_2$ to the female sex hormone; he demonstrates the presence of one carbonyl group and a hydroxyl group. The slight acidity of a solution of this compound is attributed to the

hydroxyl group (in enol form?), since ketone derivatives show no decreased acidity. The male sex hormone is extracted from male urine by the same procedure by which the FSH is derived from urine of females. On the supposition of the presence of a ketone group, a derived oxime is crystallized out of the crude extractive (organic solvents, acid or base hydrolysis). The oxime group is split off; the crystals washed and recrystallized out of dilute alcohol, and purified by double sublimation under low pressure. Fifteen mgm. of crystals were recovered from 25,000 liters of male urine. The crystalline compound has no N, is neutral in solution and saturated. The Mp is 178° C. The formula prescribed is $C_{18}H_{30}O_2$, with one hydroxyl and one carbonyl group. The biological test employed in assaying the male hormone was a modified cock's comb growth test.—M. C. Shelesnyak.

Ovarian grafts in male and female white rats (Comparación del injerto del ovario en ratas machos y hembras). del Castillo, E. B., Rev. Soc. argent. de biol. **7**: 481. 1931.

The graft takes and functions better in castrates (male or female) than in normal animals, better also in adults than in immature animals, whether they are castrates or normals. When the grafts take in normal males follicles do not mature, nor are corpora lutea formed as is seen in grafts in castrated males; hyperfeminization was not observed.—J. T. Lewis.

Clinical effects of folliculin on the arterial pressure in man (Recherches cliniques des effets de la folliculine sur la pression artérielle chez l'homme).

Action of folliculin on arterial pressure after paralysis of vagus (Les effets de la folliculine sur la pression artérielle après paralysie du vague). Daniel, C., A. Crainiceanu and L. Mavromati, Compt. rend. Soc. de biol. **106**: 997; 1000. 1931.

In women and female dogs folliculin subcutaneously or intravenously produced a small but constant fall in blood pressure whether the vagus was paralyzed with atropin or not. In men and male dogs the effect on the blood pressure was slight but inconstant. The folliculin used gave no reaction for choline. The hypotensive action of choline is abolished by paralysis of the vagus. The reduction in blood pressure in females is therefore a specific effect of the folliculin and not due to a contamination with choline.—J. C. D.

Concerning the presence of large amounts of female (sex) hormone menformon in the blood of cancer patients (males) (Über das Vorkommen von hohen Mengen weiblichen Sexual-Hormons Menformon im Blut von Krebskranken Männern). Dingemanse, E., J. Freud, S. E. de Jongh and E. Laqueur, Arch. f. Gynäk. **141**: 225. 1930.

In the blood of carcinomatous patients, both male and female, a very high content of menformon can be demonstrated, up to 10,000 units per liter instead of the normal average of 500 units per liter. The determination was made in both groups by the same method of extraction. The great difference in percentage content eliminates any question of errors in determination.

—L. C. Wyman.

Preparation of theelol. Doisy, E. A. and S. A. Thayer, J. Biol. Chem. **91**: 641. 1931.

By suitable additions to the procedure for the preparation of theelin, a new crystalline triol, theelol, has been isolated from the butyl alcohol extracts of pregnancy urine. The crystalline product was found to differ from theelin in solubility, crystalline form, specific rotation, physiological activity, and chemical composition.—S. A. Thayer.

Response of experimental cryptorchid testes of immature guinea pigs to repeated injections of urine from pregnant women (Réaction des testicules de jeunes cobayes impubères en cryptorchidie expérimentale aux injections répétées d'urine de femme gestante). Foncin, R., Compt. rend. Soc. de biol. **107**: 521. 1931.

From three to eight daily doses of 2 cc. of urine were injected into 3-weeks-old guinea pigs rendered cryptorchid. There was a rapid increase in the interstitial tissue and in the size of the seminal vesicles. These increases were

roughly proportional to the number of doses and were much more marked than found in the controls. The tubules remained infantile and spermatogenesis did not take place.—J. C. D.

The fate of transplanted testicular parenchyma (Über das Schicksal von transplantiertem Hodenparenchym). Foramitti, C., Wien. Arch. f. inn. Med. **21**: 315. 1931.

Transplanted testicular parenchyma in human subjects has been found intact in a biopsy of two patients: two and one-half years in one and in the other, eight and one-half months after operation. Auto, as well as homotransplantation, is advocated by the author.—A. Rudy.

The effect of the female hormone (menformon) on the plumage of the bird (Über den Einfluss des weiblichen [Sexual-] Hormons Menformon auf das Federkleid der Vögel). Freud, J., S. E. de Jongh and E. Laqueur, Arch. f. d. ges. Physiol. **225**: 742. 1930.

Since the purification of the female hormone has advanced so that one unit of menformon is contained in 0.0001 mgm. instead of 0.1 mgm., this substance must be tested for the presence of the same biological reactions. In order to prove that menformon is not species specific the fowl was used. Castrated Leghorn roosters were injected subcutaneously, with adequate doses, twice daily for three weeks. The site of injection was plucked and the newly developed feathering observed. In a normal or castrated male the female sex hormone feminizes the plumage. Male and female hormones influence their own group of secondary sex characters especially when these are found in the same animal. By the simultaneous injection of male and female hormones (both obtained from male urine) a gynandromorph can be produced. The hen feathering of the Sebright rooster is apparently the effect of menformon normally present. The feather type is therefore produced by this hormone of the ovary—R. B. Lutz.

Roentgen therapy in menopause. Grabowski, W., Polska gaz. lek. **10**: 909. 1931. Abst., J. A. M. A. **98**: 269.

Grabowski states that in the menopause roentgen therapy is far more economical to the patient than organotherapeutic preparations because of their price and gives satisfactory results in severe cases often unaffected by glandular substitution. The application is simple, consisting of irradiation of the pituitary body through both temples and the frontal region at intervals of three days. The series of applications is repeated every three weeks if conditions demand. Three applications are sufficient in most cases. In stubborn cases, accessory irradiation of the thyroid (after Borak of Vienna) brings speedy relief; this combination gives better results in severe manifestations. There is no danger of injury of the skin, deeper structures or brain tissue, experiments having proved that brain tissue is insensitive to roentgen rays. The thyroid is irradiated ten days after the pituitary treatment. The dose used is 180 kilovolts and 3 milliamperes through a filter of 0.5 mm. of zinc and 2 mm. of aluminum, and at a distance of 30 cm.

Morphological study of the uterine horns during sexual repose in immature, adult and castrated rabbits (Etude morphologique de l'épithélium de la trompe utérine au repos sexuel chez la lapine adulte, impubère et castrée).

The structure of the epithelium of the uterine horn during the follicular and lutein stages of ovarian activity (Sur la structure de l'épithélium de la trompe utérine pendant la période folliculaire et lutéinique de l'ova're). Guerriero, C., Compt. rend. Soc. de biol. **102**: 1072. 1929.

Under conditions of sexual rest ciliated and non-ciliated cells form the lining of the oviducts. These are equally numerous in the juxta-uterine portion but at the ovarian end the ciliated cells are more numerous. During oestrus the non-ciliated cells particularly in the portion near the uterus become distended and contain secretory granules. These are discharged during the lutein stage and the cells return to the resting state. There is no change from secretory to ciliated cells or the reverse.—J. C. D.

Cowper's gland and its reaction to castration and to different sex-hormone conditions. Heller, R. E., Am. J. Anat. **50:** (No. 1). 1932.

Cowper's glands of rats were studied in relation to the testis hormone, estrin, and the sex-stimulating principle of the hypophysis. In guinea-pigs the effects of castration were noted on these structures. In the rat castration causes a very marked degeneration after 20 days; lowering of the epithelium, a reduction in the number of tubules, and an increase in size of the lumina. After longer periods a gross decrease in size of the whole gland occurs as the number of tubules and acini decrease. In the guinea-pig less marked changes occur after 50 days. The changes noted in the rat 20 days after castration have served as a testis hormone indicator. Animals were castrated and injected for 20 days, at which time any effect of the testis extract could be noted. Preparations employed not only maintained the normality of Cowper's glands, but returned to the normal condition those of long-time castrates. Injections of estrin cause atrophy of the bulbo-urethrals. Mixtures of testis hormone and estrin produce normal glands. The gonad-stimulating extract of pregnancy urine (hebin) stimulates the development and activity of Cowper's glands. Simultaneous injections of hebin and estrin prevent the harmful effects of estrin. These data serve to substantiate the theory of the reciprocal relations of the gonads and hypophysis (Moore and Price).—Authors' Abst.

Effect of injections of urine from pregnant women on the genital tracts of the hibernating male hedge hog (Influence des injections d'urine de femme enceinte sur le tractus génital male du hérisson hibernant).

Effect of injections of urine from pregnant women on the genital tract of the hibernating female hedge hog (Influence des injections d'urine de femme enceinte sur le tractus génital femelle du hérisson hibernant). Herlant, M., Compt. rend. Soc. de biol. **106:** 1262; 1264. 1931.

Injection of urine from pregnant women into male hedge hogs shows a marked stimulation of the interstitial tissue with some enlargement of the accessory glands and little effect on the seminiferous tubules. The most marked result of similar injections in the female is an atypical enlargement of the ovarian follicules.—J. C. D.

Reactions of the ovary to injections of the placenta (Réactions de l'ovaire a des injections de placenta).

Is the substance in the placenta which reacts on the ovary a hormone of the anterior lobe of the hypophysis (La substance du placenta qui est active sur l'ovaire est-elle une hormone pré-hypophysaire)? Klein, M., Compt. rend. Soc. de biol. **102:** 1068; 1070. 1929.

Extracts from the placenta at various stages of pregnancy when injected into rabbits produce the same ovarian changes as do extracts of the anterior lobe of the pituitary. When injected into young guinea pigs, they do not produce any effect on the thyroid whereas anterior lobe extracts have a strong stimulating action.—J. C. D.

The lasting effects of transplanted testicles (Über Dauererfolge bei Hodentransplantation). Lichtenstern, R., Wien. Arch. f. inn. Med. **21:** 319. 1931.

Implanted testicles cause a lasting return of the sexual marks even several years after castration. This is demonstrated on six cases followed up several years after operation.—A. Rudy.

Note on the biological estimation of folliculin (A propos du titrage biologique de la folliculine). Lipschütz, A., Compt. rend. Soc. de biol. **102:** 623. 1929.

In mice 100 units given in one dose are less effective than 1 unit divided into 6 doses and given over a period of 60 hours. Evidently highly purified folliculin is easily destroyed by the body.—J. C. D.

Folliculin in the urine of pregnant cows (La folliculine dans l'urine de la vache gravide). Lipschütz, A., S. Veshnjakov and E. A. Wilckens, Compt. rend. Soc. de biol. **102:** 625. 1929.

Methods which yield 30,000 rat units per liter from human urine of pregnancy yield 700 or less units per liter from cows' urine.—J. C. D.

The coexistence of the male and female sex hormone (Nebeneinander männlichen und weiblichen Sexualhormons). Loewe, S., H. E. Voss and Eva Rothschild, Biochem. Ztschr. **237:** 214. 1931. Abst., Chem. Absts. **25:** 5700.

In all sex hormone preparations studied both the male and the female activity coexist. The ratio between the androkinin and the thelykinin action, as measured by tests on male and female animals, constitutes the "thely-androkinetic quotient" of the preparation. This quotient varies with each preparation and the values may differ within very wide limits. Although continued purification may leave in the preparation predominantly androkinetic or thelykinetic properties, nevertheless even the purest preparations contain the opposite sex hormone as an impurity. In the purification of thelykinin, fractions are obtained which are richer in androkinin than some original male hormone preparations. Furthermore, both in bile and in yeast the two sex hormones are present.

Parabiosis and ovarian grafts (Parabiose et greffes ovariennes). Martins, T., Compt. rend. Soc. de biol. **104:** 686. 1930.

In parabiotic female rats, one of which is castrated, a prolonged oestrous is the rule. In one pair the re-implantation of ovaries in the castrated animal produced a dioestrous condition.—J. C. D.

Effect of ovarian substances on excised rat uterus. Rosenfeld, S. and E. P. Durrant, Am. J. Physiol. **99:** 552. 1932.

The action of different sex hormone preparations upon the spontaneous rhythmic contractions of excised uteri of ovariectomized rats was studied. It was found that all ovarian tissue preparations possess inhibitory action on the rate and rhythm of these contractions while those sex hormone preparations not prepared from the ovary were without action. The dosages varied from 0.1 to 1.0 cc. in 50 cc. of the oxygenated fluid in which the contractions were measured. The effective preparations all contained corpus luteum. It is surmised that the relaxing principle is elaborated by this structure. The number of experiments made is not stated.—R. G. H.

The peroral effect of the follicular hormone (Die perorale Wirkung des Follikelhormons). Schoeller, W., M. Dohrn and W. Hohlweg, Wien. Arch. f. inn. Med. **21:** 323. 1931.

The peroral effect of the follicular hormone depends on the substances with which it is combined. The same daily dose has a greater effect when divided into small single doses. A number of experiments are cited and illustrated with charts.—A. Rudy.

Effects of continued estrin injections on young rats. Spencer, J., F. E. D'Amour and R. G. Gustavson, Am. J. Anat. **50:** (No. 1). 1932.

Daily injections of 20 rat units of estrin into young male and female rats definitely inhibits growth. It also inhibits spermatogenesis and ovogenesis. The prostate gland and seminal vesicles were castrate in type. Degenerating ova were found in the ovaries; no corpora lutea were present. These results indicate that the hypothesis of Moore and Price may be extended to include the inhibition of the growth factor of the hypophysis as well as the gonad-stimulating factors by the injection of estrin. Cessation of injections brings about the resumption of both growth and reproductive functions.—Authors' Abst

Elimination of the sex hormones by the salivary glands (Elimination des hormones sexuelles par les glandes salivaires). Trancu-Rainer, M., Compt. rend. Soc. de biol. **106:** 1001. 1931.

Young mice were injected with saliva. If this came from pregnant women, ovarian changes similar but not as marked as the usual Aschheim-Zondek reaction developed. If the saliva came from women recently delivered, the reaction was feeble. If spayed mice were used oestrus reappeared, showing that folliculin was present in the saliva.—J. C. D.

Concerning the cause of milk secretion (A propos du determinisme de la secretion lactee). Watrin, J. and P. Florentin, Rev. franç. d'endocrinol. **8:** 317. 1930.

Post mortem examination of a bitch in which milk secretion had continued for a considerable period without fecundation or gestation revealed growths in the uteri. The authors believe that for milk secretion two phases of activity are involved. One includes the development of the secreting acini, while the second is concerned with the actual secretion. It is believed that there is a uterine factor which initiates and maintains milk secretion.—B. C.

The biologic interpretation of the Zondek reaction (L'interprétation biologique de la réaction de Zondek). Watrin, M. and H. Brabant, Compt. rend. Soc. de biol. **107:** 1418. 1931.

The author presents the arguments against the hypophysial origin of the substance causing this reaction. This hormone or toxin comes from the placenta and is definitely toxic for the ovary. It may prevent follicular ripening during late pregnancy when the corpus luteum is degenerating. This would explain teleologically why it is not found in animals with short gestation periods but is present in humans and primates.—J. C. D.

Bilateral ovarian changes in unilateral injury (Doppelseitige Ovarialveranderungen bei einseitiger organschadigung und ovarielle hormonale Einflüsse auf die blutbildenden Organe). Ziegler, K., Ztschr. f. klin. Med. **118:** 124. 1931. Abst., J. A. M. A. **97:** 90.

Ziegler shows that injury of one ovary by periodic obstruction of the blood supply, but without permanent interruption of the circulation, leads to degenerative changes that may cause an accelerated life cycle and the premature death of the ovum. This process is, according to the intensity of the injury, accompanied by premature formation and maturation of follicles, and it terminates in follicle atresia; in cystic degeneration of the follicles or in progressive atrophy. In these degenerative processes, products of disintegration become liberated, and these may produce in the non-injured ovary of the other side the same degenerative processes. Moreover, in these processes a highly concentrated substance is formed and liberated which has a stimulating effect on the production of red blood corpuscles in the bone marrow. It is probable that this substance is hormonal in character and exists also during normal conditions. Its demonstration in the blood, and the extraordinarily lasting action of the injection of the smallest quantities of blood, which contain the substance, indicate that it plays an important part in the replacement of the blood lost in the cycle of the maturation of the ovum and also during labor. The development of the substance seems to be dependent on the substances from the ovum, on the follicle substance or on the follicle fluid.

The distinction between the hormone which stimulates the thyroid and the substance which stimulates the ovary as found in extracts of the anterior lobe of the hypophysis (Distinction entre l'hormone prehypophysaire excito-sécrétrice de la thyroide et le principe stimulant de l'ovaire refermé dans les extraits prehypophysaires). Aaron, M., Compt. rend. Soc. de biol. **106:** 1044. 1931.

Urine from pregnant women stimulates the ovary and not the thyroid. Anterior lobe extracts stimulate both but after certain purifications the effect on the thyroid is reduced while that on the ovary remains the same. It seems logical to assume therefore, that there are two different chemical principles involved.—J. C. D.

Effect of the anterior lobe of the hypophysis on the thyroid in guinea pigs (Action de la préhypophyse sur la thyroïde chez le cobaye). Aron, M., Compt. rend. Soc. de biol. **102:** 682. 1929.

Injections of anterior lobe pituitary extract proportional to the body weight result in a massive discharge of the thyroid colloid. There follows the histologic picture of intense rhythmic activity of the thyroid.—J. C. D.

Basal métabolism in hypophysectomized dogs (Le metabolisme basal chez les chiens hypophysoprives).

Specific dynamic action in hypophysectomized dogs (Action dynamique spécifique chez les chiens hypophysoprives). Artundo, A., Compt. rend. Soc. de biol. **102:** 650. 1929.

In five out of eight hypophysectomized dogs in good health and examined under carefully controlled conditions there was a decrease in basal metabolism. It averaged 15%. The increase of metabolic rate following eating, which has been reported decreased in such animals, was in this series slightly greater than that of control dogs when measured on a percentage basis—J. C. D.

Follicular maturation, corpora lutea and oestrous (Maturation folliculaire, corps jaune et oestrus). Brouha, L. and H. Simonnet, Compt. rend. Soc. de biol. **102:** 650. 1929.

Immature rats and mice were injected with anterior lobe pituitary extract and with urine from pregnant women. These two substances had a similar action. There was a precocious appearance of oestrous with characteristic vaginal changes and at the same time the development of large corpora lutea in the ovary.—J. C. D.

The influence of diet and the anterior pituitary growth hormone on the growth rate of adolescent rats. Bryan, A. H. and D. W. Gaiser, Am. J. Physiol. **99:** 379. 1932.

The number of days required by young male rats to grow from 60 to 200 grams has been determined in the case of 67 animals fed on a special growth diet devised by Mendel, of which 34 were injected with anterior pituitary growth hormone, and in the case of 49 animals fed on a poorer control diet, of which 27 received injections. Those receiving the special diet, diet B, and the hormone, required an average of 28 days to grow from 60 to 200 grams, those receiving diet B without injection 38 days; the rats fed on the poorer diet, diet C, and administered growth hormone averaged 37 days, and the diet C controls, 50 days. The results of Mendel which show that the special diet causes a more uniform growth at a more rapid rate are corroborated, and in addition it was found that injection of anterior pituitary growth hormone superimposed on the effects of the improved diet an even more rapid and uniform growth. Of the diet B animals 74% of the injected and only 24% of the controls required 30 days or less to grow from 60 to 200 grams, while of the diet C animals 81.7% of the injected rats and only 32% of the controls grew in less than 40 days. The body length of selected numbers of all four groups, regardless of how long it took them to grow from 60 to 200 grams, was 195 mm. within a reasonable error.—Authors' Summary (abbreviated).

Pituitary cachexia (Simmonds' disease) treated with anterior pituitary extract. Calder, R. M. Report of case. J. A. M. A. **98:** 314. 1932.

A negro farmer, aged 19, whose past health had been good and who had not been exposed to tuberculosis, had begun to suffer, five months before admission, from weakness, anorexia, nausea, gaseous eructations, constipation, loss of weight, loss of normal texture of the skin, falling of axillary and pubic hair, and decrease in libido and sexual power. Physical observations confirmed the history of loss of weight and changes in the skin and revealed weakness, apathy, subnormal temperature and low blood pressure. The sugar tolerance curve was of a mild diabetic type; the tuberculin test was positive; and the basal metabolic rate was low. The patient was treated with a commercial acid extract of the anterior lobe of the hypophysis. Under this treatment his health was apparently completely restored. The blood pressure and metabolic rate returned to normal, and he gained 16 kgm. Simmonds originally described this disease syndrome, and the experimental counterpart of the condition was produced in animals by P. E. Smith.—Author's Summary.

Finer structure of the cells of the hypophysis (Métastructure des cellules de la glande pituitaire). Collin, R., Compt. rend. Soc. de biol. **102:** 853. 1929.

Examination of stained and unstained sections from the cat by direct and indirect light confirm the author's belief that the eosinophile cells of the hypophysis during active secretion undergo transformation into basophil cells. —J. C. D.

Finer structure of the cells of the pituitary gland (Métastructure des cellules de la glande pituitaire). Collin, R., Compt. rend. Soc. de biol. **106:** 204. 1931.

Suspensions of hypophyseal cells in Ringers solution when viewed in the dark field show no distinction between the eosinophile and cyanophile cells. Treatment with Chrom-osmic gives an undistorted picture, for the outlines of a living cell and the same fixed are superimposable. Using these methods the author has traced the change from acidophile to cyanophile cells as a progressive alteration in the reaction of the granules.—J. C. D.

Dwarfism and infantilism. Cottrell, J. E., M. Clin. North America, **15:** 927. 1931.

This is a brief review of the subject with an illustrative case history. The author suggests the following classification of dwarfism and infantilism which is a modification and extension of von Hansemann's classification: (1) Dwarfism with skeletal deformity—rachitic, achondroplastic, osteomalacic, and the Morquid-Ruggles type. (2) Primordial dwarfism—with sexual development and ossification normal in proportion to age. (3) Infantile dwarfism—with absence or diminuation of sexual development and delay of ossification. The adjective "infantile" is used to emphasize the retention of characteristics of infancy or childhood. (4) Pituitary dwarfism—similar in physical constitution to the preceding type, but associated with, and presumably caused by, a destructive lesion of the anterior pituitary lobe. (5) Cretinism. (6) "Symptomatic infantilism" (not an ideal designation)—retardation of growth and development due to visceral or constitutional disease or to intoxication. Here are included cardiac infantilism, renal infantilism, intestinal and pancreatic infantilism.—I. B.

The hypoglycemic action of the hypophysectomized dog's blood. Cowley, R. J., J. Pharmacol. & Exper. Therap. **43:** 287. 1931.

A further example of some relationship between the hypophysis and carbohydrate metabolism has been brought out. The blood of several hypophysectomized dogs showed a marked hypoglycemic action when injected into normal rabbits. The effect was ascribed to an increase in a hypoglycemic, insulin-like substance or a decrease in a hyperglycemic substance. The increased tolerance to carbohydrates in hypofunction of the hypophysis, or in partial or total hypophysectomy and the hypersensibility to insulin after hypophysectomy might be explained as due to an increase in the insulin content in the blood following the decreased functioning of the hypophysis or its surgical extirpation.—R. G. H.

The method of action of pituitrin introduced into the ventricle. Cushing, H., Proc. Nat. Acad. Sc. **17:** 239. 1931. Abst., Arch. Neurol. & Psychiat. **27:** 194.

The question arises whether solution of pituitary acts peripherally after resorption into the blood stream or directly on the subependymal and thalamencephalic nerve centers. It might be assumed that the substances, after injection into the lateral ventricle, become resorbed into the blood stream either through the ependyma or the choroid plexuses. This is not probable, at least in the case of solution of pituitary, because when it is given intramuscularly or injected into the blood stream its effect is wholly different from that which follows its introduction into the ventricle. In trying to answer the question as to how the drug acts, Cushing expressed the belief that the negative responses obtained in its administration might give valuable information. These negative responses occur: (1) with insufficient dosage; (2) when the

ventricles have been greatly expanded by hydrocephalus, and (3) when the interbrain has been the seat of a tumor. The negative responses in cases of marked hydrocephalus which balloon the walls of the third ventricle and in cases of involvement of the ventricular walls by tumor serve to throw out of action the hypothalamic nuclei, the stimulation of which is assumed to call forth the typical reaction.

Concerning the occurrence, mechanism and fate of the melanophore hormone in the warmblooded organism (Über Vorkommen, Wilkungsweise und Schicksal des Melanophorenhormons in Warmblüterorganismus). Dietel-Heidelberg, Arch. f. Gynäk. **144:** 496. 1931.

Hofbauer's theory that eclampsia is the result of hypersecretion of the pituitary has called forth a lot of interest since Ehrhardt, Küstner and Biehl reported in 1927 that the circulating blood, particularly eclamptic serum contains a substance which stimulates the melanophores. This melanophore hormone is unquestionably a product of the posterior lobe of the pituitary. It must be determined which fraction of the posterior lobe component this hormone belongs to. It was determined that the melanophore reaction was specific for the posterior lobe. After several experiments, there finally was found a reliable method for extracting the hormone from the serum of humans, horses, rabbits and fowl. The hormone is excreted in the urine in varying amounts, according to the time of the day, and is also destroyed in the body. This hormone is found in the urine of men but not quite so much as in women. The melanophore hormone from the urine is efficacious in doses of 3 to 4 cm. and has a strong antidiuretic effect on rabbits. This hormone from the urine only causes water retention, which is unlike the injection of the posterior lobe extract in that the latter also causes chloride retention. In unpreserved urine, the melanophore hormone disappears rapidly and no doubt is destroyed by bacterial activity so that within 18 to 20 hours the antidiuretic effect is lost. Liver extracts are efficacious in proportion to their melanophore hormone content, just like that of the urine, although it also does have some effect on the chloride excretion. In humans, the fasting blood contains an increased amount of melanophore hormone, more so than when a lot of water has been taken. Olivet was able to find an antidiuretic substance in the urine which is identical with the melanophore hormone. From the experiments, it was determined that the melapophore hormone is a vital substance for warm-blooded animals. It belongs to the blood pressure and the antidiuresis component of the posterior lobe which diffuses in the plexus surrounding the pituitary. It is then changed in the liver, in which the effect on blood pressure and chloride excretion is lost, and is then excreted in the urine. The water excretion is dependent upon the amount of this hormone in the blood. He believes there is an active and inactive melanophore hormone in the warm-blooded animals. He stated that the blood pressure raising principle and the antidiuretic principle is unalterably combined. The melanophore hormone content of the blood and organs regulates the amount of capillary tonus and diuresis. In order to determine if there is a difference in melanophore content of the serum of normal pregnant women from 8-10 months of pregnancy and women in the very early months of pregnancy, a group of 30 patients was studied. Ten cc. of serum was used. With this method it was determined that the serum of pregnant women contained much more melanophore hormone than the non-pregnant and those in the early stages of pregnancy. In normal pregnant women there is determined an increased content of the melanophore hormone and in 10 cases of eclampsia and 4 of nephritis, only one was found who did not have a very high concentration of the hormone. In large doses, posterior lobe extract in conjunction with water intoxication produces tonic convulsions which lead to death. Frequent injections in small doses without water intoxication produces hemorrhagic or degenerative changes in the liver and kidneys. Dietel showed sections demonstrating the latter effect. The action is due to the capillary diuresis principle of the hormone. Also in eclamptic placentas, Dietel was able to obtain this hormone. He concluded, like others, that eclampsia is the result of an increased amount of posterior lobe hormone in the organism and a vicious circle is apparently present. The excessive secretion of this hormone results in damage of the capillaries with severe changes in the liver and kidneys which results in water retention and disturbance of chloride excretion. Simple hydrops gravidarum, hyperemesis, nephritis and eclampsia have apparently the same etiology and, according to the constitutional influence, present varying clinical pictures.—R. C. Moehlig.

The action of the hypertensive principle (vasopressin) and the ocytocic principle (ocytocin) of the posterior lobe of the hypophysis on the blood sugar in man (Action du principe hypertenseur [pitressine] et du principe ocytocique [pitocine] du lobe postérieur du corps pituitaire sur la glycémie chez l'homme). Gavrila, I. and G. Mihaileanu, Compt. rend. Soc. de biol. **104:** 601. 1930.

Six subjects were tested for the effect of glucose, glucose plus the hormone and the hormone alone on the blood sugar. Subcutaneous injection of vasopressin produced a definite hyperglycemia of from ½ to 2½ hours' duration, while ocytocin had no effect.—J. C. D.

The "Prolan" output of carcinomatous women after radiation treatment (Geschlechts physiologie Studien: VI. Das Verhalten und die klinische Bedeutung der Prolansauschiedung bei genital karzinomkranken Frau nach Strahlensbehandlung). Gostimirovic, D., München. med. Wchnschr. **78:** 2108. 1931.

In an attempt to localize the origin of the anterior pituitary-like substance of the urine of carcinomatous patients, the author extracted 20 fresh carcinomas by Zondek's alcohol-ether procedure. The lack of any reaction in immature female rats and mice after injections of the extractive led the author to conclude that the pituitary is the source of prolan. Seventy urine prolan analyses were made of carcinomatous patients. These were distributed in five groups. (1) before radiation treatment, (2) after first treatment, (3) before recond treatment, (4) after second treatment, and (5) a long-time post-radiation group. Sixty-three per cent of the cases in group I and 85 in groups II and III showed positive reactions. The group taken shortly after the second radiation treatment was 100% positive. After a time, the percentage decreased until a minimal level of 50% was reached after six years. The author concludes that prolan is not secreted by the tumor, but that the anterior pituitary is supposedly activated by increase in proteins or peptones. The great post-radiation increase is due either to increased cell decomposition or the direct stimulatory effects of radiation.—M. C. Shelesnyak.

Experimental studies of the anterior pituitary. I. The influence of ovarian implants on the castration cell type in the male-rat pituitary. Haterius, H. O. and W. O. Nelson, J. Exper. Zool. **61:** (No. 1). 1932.

Transplantation of rat ovaries into males was accompanied or followed within a few days by castration. Autopsy, one month subsequently, revealed, in a series of 14 experimental animals, eight successful takes and six in which no ovarian substance could be detected. Histological study of the recovered pituitaries revealed in each instance of a successful graft a total absence of castration cells, whereas in cases of non-takes the typical castration pituitary was found. In a second series, male rats castrated four months previously were implanted and allowed to live one month before autopsy. Controls were castrated at the same time as the experimental animals and sacrificed at the time of implantation. In each instance of a successful graft the pituitary picture was found to be normal, whereas non-takes and controls invariably had developed the typical pituitary of castration. Similar results were obtained in one-month castrates which had been subjected to implantation. The results obtained would indicate that ovarian substance is capable, not only of preventing, but also of correcting the castration-cell picture in a male-rat pituitary.—Authors' Abst.

Function of the hypophysis and of the region of the infundibulum and tuber in the toad, Bufo arenarum (Les fonctions de l'hypophyse et de la région infundibulo-tubérienne chez le crapaud Bufo arenarum [Hens.]). Houssay, B. A. and L. Giusti, Compt. rend. Soc. de biol. **104:** 1105. 1930.

The pars intermedia regulates the melanophores. The glandular part controls body growth and growth and activity of the sex organs. It is an antagonist of the pancreas in body metabolism. Damage to the region of the infundibulum produces polyurea and the appearance of a pellicule over the skin. Damage here also reacts on the pars intermedia.—J. C. D.

Effects of intraperitoneal implantation of hypophyses from rats castrated before puberty (Effet de l'implantation intrapéritonéale d'hypophyse de rats castrés avant la puberté). Emanuel, S., Compt. rend. Soc. de biol. **106:** 571. 1931.

Twenty-four rats of both sexes were castrated. Five to seven months later their pituitaries were grafted into immature female mice. Young females receiving pituitary grafts from normal rats were used as controls. In both cases puberty was hastened to the same degree. The ovaries of the experimental animals were much larger and showed a much greater development of corpora lutea when compared with the controls. Castration causes a distinct increase in the hypophysis of the follicule stimulating hormone and a very marked increase of the corpus luteum hormone. The formation of numerous vacuolated basophilic cells may be a histological basis for this.—J. C. D.

The hypophyseal substance which increases pancreatic diabetes (Sur la substance hypophysaire augmentant le diabète pancréatique). Houssay, B. A. and A. Biasotti, Compt. rend. Soc. de biol. **107:** 733. 1931.

Depancreatized toads cease to show diabetes after removal of the anterior lobe of the hypophysis. Transplantation of this lobe or injection of its extract results in the reappearance of the diabetes. Using over a thousand toads as tests, the author found this diabetes-producing substance present in the hypophyses of fish, of man, and of the types between. It is soluble in water and in alcohol at 60°. It is destroyed at 100°. It is non-dializable and easily adsorbed. It is a different material from the gonadotrophic substance.—J. C. D.

On the relation between the anterior pituitary body and the gonads. II. The induction of ovulation in the anoestrous ferret. Hill. M. and A. S. Parkes, Proc. Roy. Soc., s. B., London, **107:** 39. 1930. Abst., Physiol. Absts. **16:** 630.

This change may be produced by certain preparations of the anterior pituitary; other such preparations, however, may give rise to large cystic follicles or to other abnormal changes. Where ovulation occurred the accessory organs showed changes typical of oestrus and, after the ovulation, corpora lutea developed and pseudo-pregnant changes occurred in the uterus.

Hypophyseal implantation and stimulation of the sex glands and function in the toad (Implantation d'hypophyse et stimulation des glandes et des fonctions sexuelles du crapaud). Houssay, B. A., L. Giusti and J. M. Lascano-Gonzales, Compt, rend. Soc. de biol. **102:** 864. 1929.

Subcutaneous implantation of toad anterior pituitary lobe into toads stimulates the gonads of both sexes and through them the mating reactions. These are absent after gonadectomy. The glands of other forms, including the frog, are inaffective.—J. C. D.

Blood iodine in hypophysectomized dogs (La iodemia de los perros hipofisoprivos). Houssay, B. A., P. Mazzocco and A. Biasotti, Rev. Soc. argent. de biol. **7:** 450. 1931.

From 2 to 4 weeks following hypophysectomy blood iodine increases. Normal figures are found again about the sixtieth day. Afterwards the iodine content is low but within normal range. Extirpation of the posterior pituitary lobe and lesions of tuber produce an initial transitory increase somewhat less pronounced. Thyroidectomy produces a slight initial increase followed by a marked decrease in blood iodine.—J. T. Lewis.

Hyperfeminization, the anterior lobe of the hypophysis and parabiosis (Hyperféminisation, lobe antérieur d'hypophyse et parabiose). Kallas, H., Compt. rend. Soc. de biol. **102:** 621. 1929.

Eight male rats carrying ovarian grafts were parabiotically united to castrated animals. The castrated animal, regardless of sex, furnished an excess of anterior lobe hormone to its partner. This resulted in a feminization of the male as shown by an enlargement of the mammary gland. The testes shrank after a preliminary enlargement.—J. C. D.

The relation between the pituitary and tuber cinereum. The essential nature of the pituitary (Zur Frage der Korrelationsbeziehung zwischen Hypophyse und Tuber cinereum. Über die Unentbehrlichkeit der Hypophyse). Karlik, L. N. and I. A. Robinson, Pflüger's Arch. f. d. ges. Physiol. **227**: 480. 1931. Abst., Physiol. Absts. **16**: 629.

Total extirpation of the pituitary has been carried out in dogs. Animals have survived for prolonged periods and have shown a number of disturbances of function (metabolism, growth, sexual development). Removal of the lobus bifurcatus with the whole pituitary involves marked trauma to the base of the infundibulum. When the lobus bifurcatus is retained it does not hypertrophy (in animals in which the pituitary is removed). It is concluded that the pituitary is not essential to life.

Certain new observations on the action of the anterior pituitary. Kraul, L., Am. J. Obst. & Gynec. **21**: 301. 1931.

Pituitary glands obtained from rabbits, guinea pigs, rats and mice which had been treated with placental extract, placental tissue, corpus luteum hormone, folliculin, and urine of pregnant women, were implanted into immature mice. More lutein tissue and pseudocorpora could be seen in the ovaries of such mice than in those obtained from animals into which normal pituitaries had been implanted. The promotion of follicular growth by the pituitaries of animals treated with folliculin of placental tissue was variable, but occasionally increased. This phenomenon was even less pronounced after injections of placental extract, corpus luteum hormone, and urine of pregnant women. Injections of suprarenin do not increase the luteinizing action of the pituitary in transplants. Implants of guinea pig, cat, and rat placenta into immature mice have only a slight effect on the ovary. X-ray irradiation of the head does not increase the luteinizing power of the pituitary gland. On the other hand the pituitary of animals whose ovaries had been previously irradiated causes a distinct luteinization of the ovaries of the immature mice. The continuous administration of corpus luteum hormone, placental extract or tissue, folliculin, and urine of pregnant women in adult rabbits, guinea pigs, rats, or mice, causes a luteinization of varying degree, attended with an alteration, or a suppression of the ovarian cycle. The anterior pituitary does not store hormones. The human placenta at term does not contain corpus luteum hormone. The yellow body has a certain degree of independence of the ovum, as is shown by its continuing to function after removal of the latter.—Author's Summary.

The comparative action of extracts of the anterior lobe of the hypophysis on the appearance of puberty and on growth in rats and mice (Action comparée des extraits de lobe antérieur d'hypophyse sur la maturation sexuelle et sur la croissance du rat et de la souris). Lepine, P., Compt. rend. Soc. de biol. **106**: 1136. 1931.

Certain extracts of anterior lobe when injected into immature rats and mice produce a rapid maturing of the genital system without any evidence of an acceleration of general growth. The growth promoter and the accelerator of puberty are separate hormones.—J. C. D.

Effect of extracts of the anterior lobe of the hypophysis when given by mouth (Action des extraits de lobe antérieur d'hypophyse administrés par la voie digestive). Lépine, P., Compt. rend. Soc. de biol. **107**: 127. 1931.

Rabbits received extract by stomach tube and were compared with others given subcutaneous injections. The histological changes typical of anterior lobe treatment appeared in both cases.—J. C. D.

Hypophysial control of cutaneous pigmentation in an elasmobranch fish. Lundstrom, Helen M. and P. Bard, Biol. Bull. **26**: 1. 1932.

Complete hypophysectomy in the dogfish, Mustelis canis, results in pallor of the skin. This same result follows removal of the posterior (neuro-intermediate) lobe alone. Extirpation of the anterior lobe does not result in paling. Severe traumatization of the hypothalamus without destruction of the posterior lobe of the hypophysis has no influence on cutaneous pigmentation. The pallor following hypophysectomy is due to "contraction" of the cutaneous

melanophores which are normally in a state of considerable "expansion." Suspensions or extracts of dogfish posterior lobe and the commercial posterior pituitary preparations, "pituitrin," "infundin," and "pitressin" produce melanophore expansion and consequent darkening when injected subcutaneously or intramuscularly into pale hypophysectomized dogfish. Suspensions of dogfish cerebellum, skeletal muscle, and pancreas have no effect upon pigmentation. The oxytocic principle of the preparation, "pitocin," does not produce melanophore expansion in hypophysectomized fish. Administration of suspensions of dogfish anterior lobe cause a relatively weak darkening of pale fish. The melanophores of isolated pieces of dogfish skin react to these various substances in the same way as do the melanophores of fish receiving them by injection. Bright illumination of normal dogfish for several hours causes a certain degree of pallor. Covered segments of the skin pale to the same extent as exposed regions. Absence of light leads to darkening of normal fish, but darkness does not modify the pallor of hypophysectomized individuals. It is concluded that the posterior lobe of the hypophysis is responsible for the considerable degree of melanophore expansion characteristic of the skin of normal dogfish. Although the possibility of an extra-hypophysial control of cutaneous pigmentation has not been excluded, it is apparent that the pituitary gland plays a dominant role in the pigmentary alterations exhibited by the normal dogfish.
—Authors' Summary.

The centers of the hypophysis cerebri (Über die Zentren der Hypophysis cerebri. Experimentelle Untersuchung). Maiman, R. M., Ztschr. f. d. ges. Neurol. u. Psychiat. **129:** 666. 1930. Abst., Arch. Neurol. & Psychiat. **26:** 1321.

There is great interest in the question of the connections of the diencephalon and hypophysis, especially since it has been shown that diseases of the hypothalamus may produce the same picture as hypophyseal diseases. Aschner's investigations on glycosuria, those of Krehl and Isenschmied on temperature regulation, those of Leschke and Schmeider, and of von Grafe on water metabolism and those of Camus and Roussy on polyuria demonstrate the existence of vegetative centers in the hypothalamus, injury of which causes "hypophyseal" symptoms. Clinical and experimental data lead one to believe that the hypophysis and the base of the diencephalon form a unitary system. Kary (1924) destroyed the hypophysis and found degeneration (1) in the gray substance of the tuber cinereum and (2) in the ganglion supra-opticum. Pines (1925) asserted on the basis of studies by Cajal's silver methods that the anterior part of the hypophysis contains sympathetic fibers coming from the carotid plexus, and that the posterior half contains fibers coming from a nucleus in the lateral part of the base of the diencephalon; an unmyelinated bundle of fibers which descends through the infundibulum, goes to the posterior lobe of the hypophysis, forms a dense bundle there and penetrates also into the middle lobe. He called this tract the tractus hypophyseus and the nucleus of origin the nucleus hypophyseus. The latter corresponded to the nucleus paropticus, supra-opticus and ganglion opticum gasale meynerti. Greving (1926) reported that the posterior lobe of the pituitary is in connection with the nucleus of supra-opticus by means of the tractus supra-opticus hypophyseus. He could find no fibers of this tract in the anterior or middle lobes. Stengel decided that a large part of the fibers in the neurohypophysis comes from the nucleus supra-opticus, but that a part of the fibers of the posterior lobe has origin in the mesial group of spindle-shaped cells in the floor of the third ventricle. Maiman destroyed the anterior lobe of the hypophysis in three dogs, the posterior and middle lobes in three dogs and both anterior and posterior lobes in four dogs. Injury to the anterior lobe resulted in no changes in the hypothalamus. The changes in this region followed injury to the middle and posterior lobes only. The nucleus showing degeneration was the nucleus supra-opticus, and this nucleus alone. The nucleus tuveri, nucleus paraventricularis and periventricularis, nucleus mamillo-infundibularis and nucleus perichiasmaticus were all untouched after injury of the posterior lobe of the hypophysis. The nerve cell changes in the nucleus supra-opticus were characterized by a chromatolysis. In cases in which the anterior lobe of the hypophysis was removed, chromatolysis was observed in the cells of the superior cervical ganglion; whether this was present after injury to the posterior lobe was not observed. The middle and posterior lobes of the hypophysis are therefore innervated by the nucleus supra-opticus, while the anterior lobe receives its nerve supply from the carotid plexus.

The use of rabbits to test the hypophyseal hormone and that of pregnancy (Sur l'utilisation de la lapine comme test des hormones hypophysaires et gravidiques). Martins, T., Compt. rend. Soc. de biol. **107**: 180. 1931.

Removal of the hypophysis an hour after mating does not prevent ovulation, but if it is removed in less than an hour, ovulation does not occur. The response to injections of the urine of pregnancy is also rapid. Five cc. of urine which has been extracted with ether, injected intravenously into a 1 to 1½ kgm. rabbit gives definite and constant results in 48 hours. Two doses produce changes in 24 hours. Adult rabbits which have been separated from males for several weeks are entirely satisfactory.—J. C. D.

Regulation of the hypophysis by the testicle. Experiments with parabiosis (La régulation de l'hypophyse par le testicule. Expériences de parabiose). Martins, T. and A. Rocha, Compt. rend. Soc. de biol. **105**: 795. 1930.

A normal young female rat parabiotically united to a gonadectomized male or female of like age shows a precocious puberty. If the castrated male of such a pair is injected with testicular extract puberty is delayed. If a spayed female of such a pair receives injections of testicular extract, the early appearance of puberty is not interfered with. In the castrated males subjected to injections the hypophysis is normal while in the spayed females, whether injected or not, and in untreated castrated males the anterior lobe shows the characteristic ring cells of castration.—J. C. D.

The Lawrence-Biedl syndrome. McKinney, J., Society Transactions-Arch. Neurol. & Psychiat. **26**: 655. 1931.

A girl, aged 10, of Italian parentage, showing polydactylism, feeble-mindedness, retinitis pigmentosa, obesity, nystagmus and generalized choreiform movements, was presented. No other member of the family was similarly affected. A brother who died at 13 months is reported to have had 6 toes on one foot.—Author's Abst.

The effects of sustained pituitary anti-diuresis in epilepsy. McQuarrie, I. and D. P. Peeler, J. Clin. Invest. **10**: 915. 1931.

The relationship previously shown to exist between the state of hydration of the body and the occurrence of seizures in severely epileptic children has been found to hold also for early or mild cases under special conditions. Heretofore no satisfactory method has been available for the early diagnosis of the disease, especially during the long, free intervals between attacks. The present study has demonstrated, however, that convulsions or petit mal seizures can be induced almost at will in these patients by placing them on a special regimen with low mineral and relatively high water intake while administering the anti-diuretic principle from the hypophysis cerebri at sufficiently frequent intervals to prevent water diuresis. Seizures occurred regularly in a fairly large series of epileptic subjects when amounts of water equaling from two to four per cent of the body weight had been retained. Non-epileptic control subjects did not have seizures of any kind under the same or even more rigorous conditions. That the convulsive reactions so produced are not due to the direct pressor action of the extract on the cerebral vessels nor to increased intracranial pressure per se has been fairly satisfactorily shown. Under the conditions of this special procedure, the extracellular body fluids probably become sufficiently diluted to cause imbibition of a large excess of water by the brain cells. Preliminary data point to a resulting disturbance in the ionic equilibrium between the fluids on the two sides of the cell membrane. When an amount of NaCl, calculated to be just sufficient to prevent this dilution, was added to the diet, seizures either did not occur at all or occurred only after a much greater gain in weight had been produced. The more or less specific response of epileptic patients to this procedure suggests that the inherent functional abnormality of the brain cells, which is vaguely alluded to by various authors as characterizing the chronic convulsive state, may be brought to light by further investigations along this line.—I. McQuarrie.

Researches with anterior lobe of the hypophysis from urine of pregnancy and with anterior lobe pituitary substance upon various experimental animals (Über tierexperimentelle Untersuchungen mit "Hypophysenvorderlappenhormon" aus Schwangerenharn und mit Hypophysenvorderlappensubstanz). Novak, J. and H. Kun, Wien Arch. f. inn. Med. **21:** 359. 1931.

Young immature monkeys and dogs were treated with anteron which was prepared from urine of pregnancy by a commercial firm. Although details of preparation were not given, the material was stated to contain both prolan A and B. One gonad was removed from each animal for histological examination, before injection experiments were begun, for comparison with the other gonad which was examined when the animal was sacrificed after injections were completed. Details of histological examinations were given, as well as gross changes in the genitals. Follicle stimulation was more noticeable than luteinization. One male and 3 female monkeys, and 8 male and 6 female dogs were used. The dosage was varied in monkeys from 2 to 80 R.E. per kilo body weight; in the dogs 2 to 50 R.E. per kilo. In the 4 monkeys maturity was hastened proportionately to the size of the dose administered, but no harmful effect from any of the injections was noted. In dogs there was no evidence of hastening maturity, but some harmful effects on the gonads were noted. From the use of dried extract of anterior lobe no definite effects were observed. In none of the animals was there any unfavorable influence on the general health; those injected gained more weight than the controls. The suggestion is made that larger doses than have been used are necessary to produce definite effects in man. Dissimilar reactions to anterior lobe hormone in different species is well illustrated. It adds another warning against directly translating the results of animal experimentation to human problems.—J. P. Pratt.

Simmonds' hypophyseal cachexia in childhood (Simmondssche hypophysäre Kachexie im Kindersalter). de Rudder, B., Ztschr. f. Kinderh. **50:** 113. 1930.

A case is reported which occurred in a 9½-year-old girl. The diagnosis was made on the basis of dwarfism, extreme cachexia, low basal metabolic rate, small sella turcica and relative polyuria. In addition there were optic atrophy and neurological symptoms similar to those found in Frederich's ataxia.—M. B. G.

The effect of anterior pituitary lobe upon growth and fat accumulation (Über die Wirkung des Hypophysen-Vorderlappens auf Wachstum und Fettamsatz). Schäfer, W., Arch. f. exper. Path. u. Pharmakol. **160:** 628. 1931. Abst., Chem. Absts. **26:** 504.

The injection of anterior pituitary extract into female rats causes a gain in weight, not observed in normal males, but observed in castrated animals of either species. The gain is not due to an accumulation of fat. The injection of aqueous extracts prolongs the inter-estrus period.

Clinical observations on the action of the sex-stimulating hormone of the anterior lobe of the pituitary upon male genitalia (Klinische Studien über die Wirkung des Hypophysenvorderlappens auf den Männlichen Genitalapparat). Schapiro, B., Ztschr. f. klin. Med. **114:** 610. 1930.

Schapiro reports observations on 26 male patients, ranging from 9 to 29 years of age, given an extract made from the urine of pregnancy. The preparation contained the active factor related to the anterior pituitary lobe sex hormone, in a potency of 100 rat units per cubic centimeter. The diagnosis in a majority of the patients was "Dystrophia adiposogenitalis." An additional four patients studied were two of infantilism, aged 14 and 18 years, and two cases of cryptorchidism, 12 and 16 years of age. The author divided all cases into four groups: (1) Eunuchoid, (2) symptom complex: genital hypoplasia, adiposity and decreased bodily function, (3) infantilism with retarded general development, (4) cryptorchidism. In estimating the effect of the hormone, Schapiro divided the maturing effect on the genital apparatus into three phases: Grade 1 is related to growth of secondary sex characters or tendency of cryptorchid to downward displacement. Grade 2 embraces enlargement of penis and testes with spermatogenesis. Grade 3 is regarded as complete sex

maturity. In all cases Grade 1 was obtained by treatment. Fourteen patients were graded 2, and 9 graded 3. In general, the best results were noticed in patients between the ages of 15 to 18 years of age. Treatment consisted of 100 r.u. of the extract given three or more times weekly over periods of 3 months with one month interval of non-treatment. Larger doses were used in several cases, but the author warns that function may be arrested by excessively large amounts of the hormone. He cites two instances of depressed spermatogenesis in middle aged males following the administration of 1000 r.u. daily for ten days. Schapiro's significant conclusion is that the hormone is most effective in immaturity.—E. A. Sharp.

Anterior pituitary hormone in the cerebrospinal fluid during pregnancy. Soule, S. D. and T. K. Brown, Am. J. Obst. & Gynec. **23**: 44. 1932.

Cerebrospinal fluid from 5 pregnant women was injected into rabbits and the ovaries studied 36-40 hours later. From the negative results secured it appeared that the anterior pituitary hormone or at least the Prolan B is not present in the cerebrospinal fluid or, if present, is in a much less concentration than in the blood.—R. G. H.

The Lawrence-Biedl syndrome (Das Laurence-Biedlsche Syndrom). Sterting, W., Polska gaz. lek. **45**: 889. 1930. Abst., Endokrinologie, **8**: 398.

The report is made of the clinical analysis of two cases of the Lawrence-Biedl syndrome. Two boys showed abnormal general adiposity and considerable aplasia of the sex organs. There was derangement of the osseous system (hexadactylism or syndactylism) and constriction of the sella turcica, together with simple dwarfism or achondroplasia. In both cases there was lowered intellectual capacity (debility and mid-grade imbecility). There was progressive dimness of vision of the night blindness type with retinitis pigmentosa vulgaris or retinitis pigmentosa without pigment. Consanguinity and familial degeneration were definitely proven. The author believes that the dystrophia-adiposa genitalis of Fröhlich is separated from this cerebral type which is apparently caused by a constitutional defect of the diencephalon itself that is not in the gland itself but in the basal-vegetative representative (Rattners diencephalose).—Translated by J. Gagnon.

The presence of the hormone of the anterior lobe of the hypophysis which excites the secretion of the thyroid in the blood and cerebro spinal fluid, and its recovery from these fluids and from the urine (Sur la présence de l'hormone préhypophysaire excito-sécrétrice de la thyroïde dans le sang et le liquide céphalo-rachidien, et sur sa répartition dans ces milieux et dans l'urine). Van Caulaert, C., M. Aron and J. Stahl, Compt. rend. Soc. de biol. **106**: 607. 1931.

Injections of anterior lobe stimulate the thyroid in young guinea pigs. This was used as a qualitative and quantitative test. The hormone was found in the blood of man, horses, rabbits, dogs, rats, etc., in quantities which varied directly with the amount found in the urine. The hormone was likewise present in the cerebrospinal fluid but in amounts which bore no relation to those in blood or urine.—J. C. D.

Histopathology of experimental diabetes insipidus. Warner, F. J., J. Nerv. & Ment. Dis. **73**: 375. 1931. Abst., Arch. Neurol. & Psychiat. **27**: 445.

Polyuria due to puncture of the hypothalamus has been studied by Camus, Roussay, Bailey, Bremer, Curtis and others, but the histopathology of the lesions as well as their anatomic localization in the hypothalamus has not been studied. Two dogs are described in which after complete hypophysectomy by the transpalatosphenoidal route polyuria developed. The lesion in one dog was situated in the anterior part of the hypothalamus, the lowest and largest lesion being situated in the area of the preoptic and anterior hypothalamic nuclei, the filiform nucleus and dorsal tip of the dorsomedial hypothalamic nucleus. The lesion in the second dog was situated in the hypothalamus just anterior to the infundibular stalk, involving the nucleus tuberis. Enormous proliferation of microglia, with gitter cells and macrophages, were found microscopically in these spots. Proliferation of new vessels and degeneration of ganglion cells were noted. In both dogs there was no marked metabolic dis-

turbance in spite of complete extirpation of the hypophysis. The experiment indicates the presence of centers in the hypothalamus that may control the urinary output by regulating the metabolism of water and also that it is the injury to the hypothalamus rather than the hypophysectomy that causes the permanent polyuria. The latter conclusion the author draws from the fact that in only one of the animals was the hypothalamus injured at the time of the hypophysectomy, and this was the only one to develop permanent polyuria. The first hypophysectomized animal, in spite of four hypothalamic punctures, did not develop permanent polyuria. These observations agree with Leschke, Camus and Roussy who, however, did not make accurate neurologic studies of the brains of their animals.

Comparison of the capacity of anterior hypophyseal tissue of mature and immature female rabbits to induce ovulation. Wolfe, J. M. and R. Cleveland, Anat. Rec. **51**: (No. 2). 1931.

A saline suspension was prepared from the anterior-lobe tissue of both sexually mature and sexually immature female rabbits. One cubic centimeter of the suspension was equivalent to 1 mgm. of fresh tissue. This suspension was injected into the marginal ear vein of sexually mature female rabbits. Injections of 2.5 mgm. of fresh tissue from both mature and immature rabbits induced ovulation. In either case, however, it was necessary to inject 5 mgm. to obtain the result consistently. Anterior-lobe tissue from very young female rabbits (four to five weeks) was apparently deficient in the factor causing ovulation.

Enteral administration of insulin to normal dogs. Bollman, J. L. and F. C. Mann, Am. J. M. Sc. **183**: 23. 1932.

Large amounts of insulin may be instilled directly into the duodenum, jejunum or ileum without any appreciable effect on the sugar of the blood of normal dogs, except for the slight effects when concentrated insulin was used. The addition of acid, blood or bile to insulin thus administered did not alter this. If insulin is injected into the lumen of an isolated portion of ileum the blood sugar of the animal is not affected, but small amounts of insulin given submucously produce typical hypoglycemia. Insulin gradually disappears from within the lumen of the ileum. With the doses we have used, sufficient insulin remains after one hour to produce definite hypoglycemia if injected subcutaneously. Insulin incubated with ileac washings is not so rapidly destroyed. It would appear that the intestinal mucosa inactivates insulin so that it is not effectively absorbed. Small amounts of insulin may escape inactivation if sufficiently concentrated insulin is applied to the intestine.—Authors' Summary.

Action of vagotonin on glycemia (Action de la vagotonine sur le glycemie). Brieu, T., F. Fuchs, D. Santenoise and M. Vidacovitch.

Insulin and liver glycogen (Insuline et glycogene hepatique). Santenoise, D., H. Verdier and M. Vidacovitch, Compt. rend. Soc. de biol. **104**: 768; 773. 1930.

These are reviews of the work done and evidence in favor of the dual nature of the pancreatic hormone with the suggested name of vagotonin for the newly isolated one. Vagotonin, compared to insulin, has a less marked hypoglycemic action. This is slower to appear but lasts longer. Insulin has no effect on liver glycogen, while vagotonin increases it. Early investigators with insulin were dealing with these two hormones together and the results reported by them represented a combined action.—J. C. D.

Endocrine function of the pancreas and calcium metabolism (La fonction endocrine du pancreas et le metabolisme du calcium). Cahane, M., Rev. franç. d'endocrinol. **9**: 383. 1931.

In a study of 13 diabetics no significant correlation was discovered between the blood sugar and the blood calcium levels. In 9 cases treated with insulin there was no evident relationship between changes in sugar level and the blood calcium.—R. G. H.

Contraction of the spleen induced by insulin (Contraction de la rate provoquée par l'insuline). Ionesco, D., A. Bernard and M. Enachesco, Compt. rend. Soc. de biol. **102:** 1107. 1929.

In 11 dogs intravenous injections of insulin produced a marked contraction of the spleen. This occurred even after removal of the adrenals and was not due to cholin in the insulin.—J. C. D.

Variations in gastric secretion during insulin hypoglycemia (Les variations de la sécrétion gastrique au cours de l'hypoglycémie insulinique). La Barre, J. and C. des Cespédes, Compt. rend. Soc. de biol. **106:** 480. 1931.

Dogs with a permanent gastric fistula were used. Injection of insulin was followed by increased gastric movements, increased secretion of gastric juice and increased hydrochloric acid contents of the gastric juice.—J. C. D.

Variations in insulin secretion during intrapancreatic hyperglycemia (Les variations insulino-sécrétoires au cours des hyperglycémies intrapancréatiques).

Variations in insulin secretion during extrapancreatic hyperglycemia (Les variations insulino-sécrétoires au cours des hyperglycémies extrapancréatiques). La Barre, J., Compt. rend. Soc. de biol. **106:** 1244; 1247. 1931.

The carotid of a depancreatized and hyperglycemic dog A was connected to the pancreatic artery of dog B. The vagi of B were cut and the pancreatic vein drained into the circulation of dog C, whose pancreas was isolated from his circulatory system. The excess of sugar circulating through the pancreas of dog B failed to reduce the blood sugar in C. Therefore intrapancreatic hyperglycemia does not result in any large output of insulin. In a similar series of three dogs in which the nervous connections of the pancreas in dog B are intact when the blood sugar is increased in dog B, although none of it circulates through C's pancreas there is an increased output of insulin as shown by the hypoglycemia in dog C.—J. C. D.

Oral administration of bismuth-insulin for gastroduodenal troubles (Ueber perorale Behandlung der gastroduodenalen Geschwuere mit Bismutinsulin). Levai, M., Wien klin. Wchnschr. **44:** 1112. 1931.

Levai treated 11 cases of duodenal ulcer and one of gastric ulcer with a suspension of bismuth-insulin given orally, and obtained good results. He used a bland diet the first week only, as a precaution. The action of the insulin is supposed to be catalytic. Its effect does not depend on its quantity. Two cases with healing of the ulcers, as shown by the x-ray findings before and after treatment, are reported in full.—A. Rudy.

Diabetes mellitus with resistance to insulin and failure to obtain clinical improvement from its use. Report of cases. Mohler, H. K. and H. L. Goldburgh, M. Clin. North America, **15:** 343. 1931.

A case is described in which a known diabetic with an enlarged cirrhotic liver, who had been controlled adequately by diet, developed an acute exacerbation of an old tuberculous process of the lung, and suddenly required massive doses of insulin to control the blood sugar. In spite of this control the clinical condition became progressively worse. The cause of death in this patient was not diabetes, but the associated disease which interfered with the action of insulin. The patient was able to tolerate between 80 and 100 gm. of carbohydrate between the second and tenth month of his known tuberculosis without the use of insulin. An undetermined crisis developed 40 days preceding death which finally necessitated massive doses of insulin. He received a total of 17,515 units of insulin over a period of 40 days or an average of 437 units a day. The highest dosage of insulin given in a day was 1150 units on a carbohydrate intake of 92 gm. Two other cases are reported in which diabetes mellitus was present but was not responsible for the death of the patients. The use of insulin, although controlling the glycosuria and blood sugar, did not produce clinical improvement and for a time the physicians believed that although the insulin caused the urine to become sugar free and the blood sugar to return to normal it failed to be beneficial to the diabetic.

Subsequent events proved that a disease other than diabetes was the cause of death. When a diabetic does not show clinical improvement with a balanced weighed diet and adequate insulin therapy, even though the blood and urine are normal, one should seek for other causes than diabetes to explain the downward course of the disease. It has not been proved that uncomplicated diabetics are resistant to insulin. Diabetics requiring insulin invariably need insulin at least once daily. The practice of giving small doses of insulin to diabetics every two or three days is almost valueless.—I. B.

Diabetes mellitus and pregnancy. Peckham, C. H., Bull. Johns Hopkins Hosp. **49:** 184. 1931.

A study of 17 pregnancies in 12 diabetic women indicates that the diabetes may become somewhat aggravated during the first two-thirds of pregnancy, but a definite improvement is to be expected as the patient approaches term. Death of the foetus in utero may result in an immediate break of the diabetes from control. The course of labor in such patients is not unfavorable and the puerperium seems to present no particular danger. A hypoglycemia during the early puerperium may become evident. The improvement noted during the last part of pregnancy may persist for some weeks or months after delivery. The duration of such improvement is often coincident with lactation, and nursing may be safely continued as long as possible. Toxemia is a frequent complicating factor. The outcome to the child is not unfavorable. Under careful supervision, there seems to be no reason why the average diabetic woman should not pass through a restricted child-bearing career with a reasonable degree of safety.—Author's Summary.

Action of insulin on intra-ocular pressure (Über die Einwirkung des Insulins auf den intraokilaren Druck). Räiha, C. E. and L. Grönlund, Skandinav. Arch. f. Physiol. **62:** 70. 1931. Abst., Physiol. Absts. **16:** 623.

Intra-ocular pressure was measured at intervals of 5 minutes in rabbits by means of a Schiötz tonometer after application of a local anaesthetic to the conjunctiva. After intravenous injection of insulin there is an initial fall of intra-ocular pressure, followed by a transient rise, which gives way to a fall of long duration; the fall may be explained partly by the action of insulin on the cardiovascular system, partly by an effect suggesting increased excitability of the parasympathetic system.

Association of vagotonic pancreatic extract (vagotonic hormone) with insulin in diabetes (Premiers resultats obtenus chez certains diabetiques par l'association de la vagotonine a l'insuline). Santenoise, D., T. Brieu, G. Fuchs, P. Louyot and M. Vidacovitch, Rev. franç. d'endocrinol. **9:** 259. 1931. Abst., J. A. M. A. **97:** 1745.

Santenoise and his co-workers have shown that the pancreas plays an important part in the regulation of reflex excitability and pneumogastric tonus. The pancreas introduces into the circulation a substance that regulates the activity of the vagus nerve. Purified insulin is not vagotonic as is usually believed; that property is a function of another hormone. They have extracted from the pancreas a substance presenting all the characteristics of true hormones and endowed with considerable pneumogastric activity. The substance differs from insulin in biologic, chemical and physicochemical characteristics and has been designated by Santenoise in 1922 as a pancreatic vagotonic hormone. Insulin demonstrated vagotonic properties when it was not pure and contained the accessory hormone. This vagotonic hormone seems to be a regulator of glycogen through its influence on the vagus nerve. There is a dual action in the glycoregulatory hormones of the pancreas; the vagotonic hormone regulates the anabolism and insulin the catabolism of carbohydrates. The addition of the hormone increases the action of insulin. Their glycoregulatory action is synergistic and complementary. The results obtained when the two hormones were associated in the treatment of diabetes were conclusive. In summary, the addition of the vagotonic hormone to insulin in the treatment of some diabetic persons increased the glycoregulatory function of the pancreatic extract, the quantity of insulin necessary was diminished and the number of daily injections sometimes cut to one; increased carbohydrate tolerance made possible an increased intake of sugar; the glycosuria and acetone bodies disappeared; the lipoid and protein metabolism was improved; there was an

increase in weight and an improvement in the general body condition. More than 30 patients with diabetes were treated in this way. The authors believe that their results recommend the association of the vagotonic pancreatic extract with insulin in the treatment of diabetes.

Aspects of diabetes with insulin resistance (Zur Kenntnis des insulinresistenten Diabetes). Serio, F., Klin. Wchnschr. **10**: 1998. 1931. Abst., J. A. M. A. **97**: 1932.

Serio states that patients with the form of diabetes which is resistant to insulin usually appear well nourished, have only slight acidosis and are influenceable only slightly by dietetic measures. He then describes the clinical history of such a patient. Since dietary measures as well as insulin therapy failed in their effect and since the patient showed slight symptoms of hyperthyroidism, an antithyroidal preparation was administered in increasing quantities. After 40 days of this medication the insulin resistance had completely disappeared, so that 14 units of insulin was now sufficient to reduce the glycemia considerably and even to produce hypoglycemic symptoms. The sugar content of the blood during fasting became normal and could be kept in normal limits in spite of a free diet and of tolerance tests, even after the treatment had been discontinued. The renal elimination of sugar continued. This was probably due to a renal factor, which became evident after the hyperglycemia had disappeared.

The coincidental occurrence of diabetes mellitus and pernicious anemia. Shookhoff, C., Ann. Int. Med. **5**: 116. 1932.

Two cases of the coincidental occurrence of diabetes mellitus and pernicious anemia are reported; one in whom the diabetes antedated the pernicious anemia by eight years, and the other in whom both diseases were found simultaneously. Liver and insulin were given to both patients. In Case I the diabetes became more severe at a time when the patient had entered into a remission of the anemia; in Case II the anemia did not respond well to specific treatment, while the diabetes was always easily controlled by insulin and diet. No relationship seems to exist between pernicious anemia and diabetes, nor does the presence of one disease affect the course of the other in a characteristic manner. Results of specific therapy, when a sufficiently large number of patients having both diseases have been treated, may give some information as to the relationship of these diseases. In the few cases so far studied uniform results have not been obtained—Author's Summary.

The mechanism of splenic contraction produced by insulin in dogs (Sur le mécanisme de la contraction de la rate du chien provoquée par l'insuline). Teitel-Bernard, A. and C. Parhon, Compt. rend. Soc. de biol. **107**: 185. 1931.

In four dogs the spleen was isolated from the circulatory system but the nerve supply left intact. Insulin injected into the general circulation did not produce a splenic contraction while insulin perfused through the spleen did. —J. C. D.

Spontaneous hypoglycemia (Insular Hypercrinia). Valenzuela, O., Rev. Medicina de Chile, Sept., 1931.

The case is reported of a man of 24 who developed tonic and clonic convulsions leading to a diagnosis of epilepsy, then hysteria. He failed to respond to treatment directed toward either condition. It was then discovered that the convulsions were related to hunger and the blood sugar was found to vary from 0.083-0.035 gms. per cent. Ketone bodies appeared in the urine at the end of convulsive fits. Administration of adrenal, pituitary and thyroid extracts were not efficacious. Glucose injections had a minimal effect on the blood sugar. The etiology is assumed to be oversecretion of insulin.—R. G. F.

Inactivation of crystalline insulin by cysteine and glutathione. du Vigneaud, V., Alice Fitch, E. Pekarek and W. W. Lockwood, J. Biol. Chem. **94**: 233. 1931.

The reduction of crystalline insulin by such mild reducing agents as cysteine and glutathione has been studied. It was found that under definite conditions as to concentration and hydrogen ion concentration that the insulin was

completely inactivated by both cysteine and glutathione. Attempts to reactivate the material by mild oxidation were uniformly negative. The evidence pointed towards the fact that the reduction of the disulfide grouping was the cause of the inactivation and that the sulfhydryl form of insulin is inactive. The insulin inactivated as above failed to yield the head precipitate which is so characteristic of insulin. It was also found that insulin is soluble in dry liquid acetamide and in liquid ammonia. The inactivated material is practically insoluble in dry liquid acetamide.—Authors' Abst.

Diabetes mellitus and the gastric secretion. Wohl, M. G., J. Lab. & Clin. Med. **17:** 22. 1931.

This paper reports the results obtained in studying the gastrointestinal function of a group of diabetic patients. The gastric contents were studied by the fractional method in 33 cases, 19 of whom manifested some gastrointestinal symptoms. Roentgen examinations were made in 12 patients and in 24 the stools were examined. In 10 the duodenal contents were studied for the presence of pancreatic ferments. Eleven patients showed an achlorhydria and seven hypoacidity. Four had an hyperacidity while 11 patients had an acidity within the normal range. Of the latter four had some gastrointestinal complaint. This work indicates that the occurrence of achlorhydria and hypoacidity in diabetes mellitus is of greater frequency than normally found. The author concludes therefore that attention should be given to the gastrointestinal tract in the treatment of patients with diabetes mellitus and suggests that the administration of dilute hydrochloric acid in addition to the diabetic regimen may lessen the gastric complaints of such persons.—H. C. Shepardson.

Parathyroidectomy and vitamin D (Parathyroïdectomie et vitamine D). Arthus, A. and A. Jedrzejowska, Compt. rend. Soc. de biol. **107:** 23. 1931.

In rabbits fed on a diet rich in vitamin D previous to parathyroidectomy, tetany and death do not follow the operation.—J. C. D.

Parathyroid gland and calcium metabolism. Ask-Upmark, E., Hygiea, **93:** 704. 1931. Abst., J. A. M. A. **97:** 1842.

Ask-Upmark states that, in 63 out of 92 cases of parathyroid enlargement from the literature or from personal observation, there were diseases of the bones, 48 of the cases being instances of osteitis fibrosa generalisata. The parathyroid enlargement, practically always present in this disease, is probably to be regarded as a toxic adenoma primary to the disturbance in the bones and in the mineral metabolism. In the differential diagnosis of osteitis fibrosa generalisata, exploratory operation on the parathyroids should be done if necessary; and palpation of the neck, and particularly determination of the blood calcium are advised in all cases of more generalized involvement of the bones. Removal of the parathyroid adenoma (Mandl) has been done, with improvement in 16 cases.

The effect of irradiated ergosterol on tetany resulting from parathyroidectomy in rabbits (Influence de l'ergostérol irradié sur la tétanie consécutive a la parathyroidectomie chez le Lapin). Lesne, E., R. Dubois and H. Simonnet, Compt. rend. Soc. de biol. **107:** 441. 1931.

One hundred grams of irradiated ergosterol a day were given by mouth to 21 rabbits following parathyroidectomy. Ten died during treatment but the average life span was 17 days instead of 4, as was the case with the untreated animals. Five died after cessation of treatment. In all these animals there was a reduction in blood calcium exactly as in untreated animals in the few days following parathyroidectomy. The rabbits receiving ergosterol did not die during this phase as did those not receiving it.—J. C. D.

Effect of parathyroid extract injected into the cerebro-spinal fluid (Effet de l'extrait parathyroïdien injecté dans le liquide céphalorachidien). Nitzescu, I. I., Compt. rend. Soc. de biol. **102:** 1123. 1929.

The extract passes through the choroid plexus and produces a rise in blood calcium in dogs.—J. C. D.

On relation between parathyroid hormone and growth of rat carcinoma. Paik, T. S., Am. J. Cancer, **15**: 2756. 1931. Abst., J. A. M. A. **97**: 1738.

Paik describes experiments on rats in which he demonstrated that there is a close relationship between the growth of transplantable rat carcinoma and the internal secretion of the parathyroid. The internal secretion of the parathyroid stimulates the development of rat carcinoma, but decrease of its internal secretion interferes with development of such a carcinoma.

Osteitis fibrosa cystica of the skull associated with heminaopia psychotic symptoms. Palmer, H. D., R. Harrow and L. A. Schwartz, Arch. Neurol. & Psychiat. **27**: 45. 1932.

The case reported is one of localized osteitis fibrosa cystica resulting from an injury to the skull in infancy and giving rise to neurologic symptoms twelve years after the occurrence of the trauma. The etiologic rôle of the trauma is significant since recent literature has tended to designate the generalized form as dependent on parathyroid hyperplasia and the local type as determined purely by trauma. Yet it is obviously very rare that bone injury alone leads to the formation of cystic areas of osteitis. In the light of recently established relationship between endocrine imbalance and the malacias, it may be conjectured that there are conditioning endocrine factors in patients who develop cystic bone lesions following a trauma, resulting in a disordered metabolism and predisposing to anomalous repair with typical cyst formation.
—Authors' Summary.

Increase in the transparency of bones when x-rayed, after injections of Collip's parathormone (Augmentation de la transparence osseuse auz rayons X, a la suite d'injections de la parathormone de Collip). Parhon-Stefanesco, C., Compt. rend. Soc. de biol. **108**: 300. 1931.

An epileptic received a total of 1200 units over a period of seven weeks. There was a progressive decrease in the density of the bony shadows.—J. C. D.

The spleen, an endocrine organ (La rate consideree comme un organe a secretion interne [A propose d'un recent article de G. P. Sakharoff]). Manoukine, J., Rev. franç. d'endocrinol. **8**: 527. 1930.

The author calls attention to the oversight by Sakharoff of his work on leucocytolysin and antileucocytolysin from the spleen and liver, respectively.
—B. C.

Influence of castration on the involution of the thymus (Influence de la castration sur l'involution du thymus). Jolly, J. and C. Lieure, Compt. rend. Soc. de biol. **102**: 762. 1929.

Castration in male guinea pigs slightly before maturity (16 animals) delayed somewhat the normal involution of the thymus.—J. C. D.

Studies on the histogenesis of the thymus. Histologic reconstruction of thymus grafts (Recherches sur l'histogenèse du thymus. Reconstitution histologique du thymus greffé). Lieure, C. and O. Bonciu, Compt. rend. Soc. de biol. **106**: 644. 1931.

Grafts placed under the skin of the thigh or between the muscles of the abdominal wall of young guinea pigs were followed for three weeks. The thymocytes and Hassals corpuscles disappear and there is a certain amount of destruction of the reticulum. Most of the reticular cells survive, however, and about the fifth day form compact clumps. Mitosis increases in these clumps and mononuclear cells appear in great numbers. Hassals corpuscles are laid down in the interior of the clumps and entirely without relation to the vascular system. Reconstruction is complete about the third week.—J. C. D.

The physiologic and pathologic rôle of the thymo-lymphatic system (Le rôle physiologique et pathologique du systeme thymo-lymphatique). Mouriquand, G. and M. Bernheim, Acta Pediatrica, **11**: 286. 1931.

The existence of the thymo-lymphatic system has not been proven. There seems to be no relationship between the spleen, lymphatic glands or thymus histologically, embryologically or physiologically. The only rôle in which there

is a relationship between both systems is that of biochemical composition. It is difficult to deny the existence of this syndrome clinically but the rôle of the thymus and of its hypertrophy is the subject of much controversy. The origin is either a constitutional state or a congenitally acquired state in utero due to several factors, among them infection. The authors favor the latter and feel that, whatever the origin, the infant with this status is born with a dystrophy favorable to sudden death.—M. B. G.

Ketonuria in experimental hyperthyroidism (Uber Ketonuria bei experimenteller Hyperthyreose). Abelin, I. and A. Jordi, Ztschr. f. ges. exper. Med. **68:** 20. 1929.

Administration of thyroid substance or injection of thyroxin produces an increase in excretion of acetone, aceto-acetic acid, and B-hydroxylbutyric acid in the urine. This increase is due in greater part to the B-hydroxylbutyric acid than to the total acetone excretion. Analogous to the effect of thyroid substance on the gaseous and nitrogen metabolism the ketonuria will also be first noticeably increased within a period (4 to 5 days generally) after the beginning of thyroid administration. The maximum ketonuria was observed on the 10th to 14th day of thyroid administration. Thyreotoxic ketonuria does not show a straight line; rather after several days of increase there follows a period of lowered ketone excretion. One finds analogous variations in the gas metabolism and protein catabolism after thyroid administration. This zig-zag course of the metabolic process shows definitely that during the course of experimental hyperthyroidism the organism itself is able to make considerable compensation. After administration of thyroid substance the purely quantitative effect on ketonuria is rather small; it is much weaker than it is after phloridzin or alkali medication. This fact is traceable to the lack of fatty degeneration of the liver in experimental hyperthyroidism, for usually fat deposition in the liver belongs to the picture of most ketonurias.—I. B.

Influence of roentgen irradiation of thyroid on deaminizing functions of liver in exophthalmic goiter (L'influenza della roentgenterapia tiroidea sulla funzione deamminante del fegato dei basedowiani). Alzona, L., Riforma med. **47:** 1323. 1931. Abst., J. A. M. A. **97:** 1420.

Alzona concludes from his detailed study of eight cases of exophthalmic goiter that: Irradiations of the thyroid with inhibitive doses in patients with exophthalmic goiter cause inconstant changes of the amino-acidemic curve provoked. Such changes, when present, indicate a variation in the functioning of the liver in exophthalmic goiter patients, as a result of therapeutic roentgen applications, in the sense of a diminished deaminizing functioning of that organ. There is not a parallel relation between the intensity of the variations of the amino acid curve and the improvements secured from the roentgen treatment. Such changes show that a diminished functioning of the thyroid is usually associated with a lessened efficiency of the deaminizing function (and hence of the hepatic function), which fact confirms in a measure the theory recently proposed by Pende concerning hepatothyroid synergism.

The demonstration of the hormone of the thyroid gland in the blood of pregnant women and the influence of the heightened function of the thyroid gland on metabolism, circulation and nervous excitability in pregnancy (Über den Nachweis des Schilddrüsenhormons im Schwangerenblute und über den Einfluss der gesteigerten Schilddrüsenfunktion auf Stoffwechsel, Kreislauf und Nervenerregbarkeit in der Schwangerschaft). Anselmino, K. J. and F. Hoffman, Arch. f. Gynäk. **145:** 114. 1931. Abst., Chem. Absts. **25:** 5698.

During pregnancy there is an increased combustion of carbohydrates and a decrease in the glycogen supply of the organism as glycogen is mobilized from its storage depots and the formation of glycogen from the sugar of the food is hindered. There is an increased formation of lactic acid from breaking down of glycogen with an increased lactic acid content in the blood. There is also an increased formation of acetone bodies, indicating that the glycogen supply is low. Alimentary glucosuria is readily induced. All these effects are also seen with hyperthyroidism, experimentally induced or in Basedow's disease, and may be interpreted as due to an increased content in the blood of the hormone of the thyroid gland. In the anomalies in metabolism, circulation

and nervous excitability shown in pregnancy, the resemblance is close to a mild case of Basedow's disease. In a normal pregnancy, however, this increase in activity of the thyroid gland is a physiologic process.

Thyrotoxicosis with a normal metabolism early in the course of the disease. Ball, F. E., M. Clin. North America, **14**: 1277. 1931.

This brief paper consisting essentially of three illustrative case histories is one of quite a number appearing throughout the world to indicate that thyroid overactivity, especially in its early stages, is not necessarily associated with a metabolic rate above the conventional normal. It is also pointed out that one metabolic test should be taken with the proverbial grain of salt in any given case. Many patients hastily regarded as suffering from neurasthenia or a form of neurosis are really sufferers from thyrotoxicosis unconfirmed by a heightened metabolic rate. Occasionally, the cautious administration of iodine in these cases serves as a therapeutic test.—I. B.

The condition of the calcium in the blood serum of normal and parathyroprivic dogs (Der Zustand des Ca in Blutserum von normalen und parathyreopriven Hunden). von Beznak, A., Biochem. Ztschr. **225**: 295. 1930.

The total content of Ca in the serum of normal and parathyroprivic dogs was determined by the method of Kramer and Tisdall. The serum was shaken with 10% of powdered bone and the Ca remaining determined. The difference gives the adsorbed Ca. In normal dogs this is about 40%; in the parathyroprivic animals, about 30% of total. The absolute value fell from 4.89 mgm. % in normals to 2.64 mgm. % in the operated animals, a change of 60%. While the value of the total Ca changed only 35% (11.8 mgm. % to 7.5 mgm. %, the amount of adsorbable Ca shows greater variability, 0-50 mgm., than the normal, 31-51 mgm. The severity of the tetanic symptoms corresponds to the decrease in adsorbable Ca. No difference was found in the ability of bone powder derived from normal and parathyroprivic dogs to adsorb Ca nor was it shown that the Ca complex of parathyroprivic animals was more adsorbable. The decrease in Ca is due to a decreased formation of the negatively charged complex which holds Ca in solution.—J. M. Looney.

The amount of physiological diffusible calcium in serum of normal and parathyroprivic dogs (Die Menge des physiologisch diffusiblen Ca in Serum normaler und parathyreopriver Hunde). von Beznak, A., Biochem. Ztschr. **225**: 305. 1930.

The total Ca and the Ca adsorbable by powdered bone were determined in the serum and lymph from the thoracic duct of normal and parathyroprivic dogs. The total Ca (8.75 mgm.) in the lymph is 87% of that in the serum (9.97 mgm.) in the normal dog, and 86% in the operated dogs: Lymph, 4.46 mgm.; serum, 5.18 mgm. The adsorbable Ca is 42% of the total Ca in the blood serum of normal dogs and no adsorbable Ca is found in the lymph. As the lymph contains 83-90% of the amount of blood serum Ca the author concludes that all the Ca present in the blood serum is diffusible. The physical chemical condition of the Ca is the same in serum and lymph of both normal and operated dogs. Parathyroidectomy does not change the diffusibility of the Ca of the blood serum.—J. M. Looney.

The effect of parathyroidectomy on the sedimentation rate of the red blood corpuscles (Die Wirkung der Parathyreoidectomie auf die Senkungsgeschwindigkeit der roten Blutkorperchen). von Beznak, A., Biochem. Ztschr. **225**: 312. 1930.

The parathyroid glands of three rabbits were removed without disturbing the thyroid. The thyroid and parathyroid glands of six dogs were also removed. In all cases the sedimentation rate was greatly accelerated. This result was due to the decrease in the negatively charged Calcium complex. As the experiments were performed in oxalated blood the result could not be due to differences in Calcium ion concentration.—J. M. Looney.

Iodine content of blood, especially in exophthalmic goiter. Billmann, C., Hospitalstid. **74**: 395. 1931. Abst., J. A. M. A. **97**: 362.

Billmann found the iodine content of the blood in 10 normal persons to be from 0.008 to 0.018 mgm. per 100 cc. In patients with non-toxic goiter the iodine value of the blood was normal. In patients with thyrotoxicosis, it was increased by from 0.01 to 0.154 mgm. per 100 cc. The possibility is suggested that determinations of the iodine content of the blood may enable one to diagnose exophthalmic goiter before a definite increase in the basal metabolism occurs.

Low basal metabolic rates in constitutional asthenics without hypothyroidism. Blumgarten, A. S., M. Clin. North America, **14**: 1377. 1931.

This important contribution discusses the various phases of apparent hypothyroidism in which there is an associated low basal metabolic rate without tangible evidences of hypothyroidism or myxedema. These patients do not respond to thyroid opotherapy, but, on the contrary, may present toxic symptoms from thyroid medication. Hypothyroidism and myxedema do not stand alone in the presentation of a low metabolic rate. Malnutrition and starvation, Addison's disease and hypopituitarism present abnormally low metabolic rates. Also, in children between the ages of 8 and 14, the B.M.R. may be as low as minus 18 to minus 20% without evidence of disease. Indeed, instances of juvenile exophthalmic goiter may present a basal metabolic rate quite within the conventional normal, which would indicate that the actual normal metabolic rate in young patients is considerably below what is ordinarily looked upon as the standard. Five patients described by the author were constitutional asthenics presenting a varying symptom-complex of autonomic dysfunction. Their chief complaints were such inconstant manifestations as stomach trouble, headache, nervous breakdown, and heart hurry. The constant factors in all cases were asthenia, low blood pressure, emotional instability, underweight and a low basal metabolic rate. However, similar cases present themselves in which the B.M.R. was within normal limits. It cannot be denied that the low B.M.R. suggests a possible endocrine factor to explain the symptoms. The therapeutic test is of importance in discrimination of these cases from those which are due primarily to thyroid underfunction. The author believes that possibly the pathogenesis of these cases resides in chronic adrenal insufficiency.—I. B.

Iodine metabolism and excretion after intravenous administration of thyroxine. Boe, J., Polska gaz. lek. **10**: 925. 1931. Abst., J. A. M. A. **98**: 518.

Boe conducted several experiments, using his collaborators, who were placed on an iodine constant diet for two weeks, to find the action of organic iodine, thyroxine in this case, on iodine metabolism in the tissues and its elimination by secretion and excretion. The observations, made after intravenous injection of 2 mgm. of thyroxine, are as follows: The iodine level returns to normal after from two to three hours; the increase of iodine level in the blood is caused by alcohol insoluble element, while the alcohol soluble element remains unchanged; one-fifth of the injected iodine is excreted in the urine; the excretion curve is almost parallel to the curve in the blood. All traces of iodine disappear from the urine in twenty-four hours.

The value of the cholesterol determination in thyroid patients (Der Wert Der Cholesterinamie in den Schilddrusenkrankheiten). Bonilla, E. and A. Moya, Endokrinologie, **9**: 171. 1931.

The authors record the basal metabolism, pulse, blood pressure and body weight along with the blood cholesterol in 11 cases of hyperthyroidism, four cases of simple goiter and five cases of myxedema. They conclude that the function of the thyroid has no influence on the blood cholesterol. They state that the hypothesis of Lande and Guy Laroche, namely, that the thyroid does influence cholesterol metabolism, has been completely refuted by their findings. They further conclude that there is no prognostic value in the determination of the blood cholesterol. They believe their work also furnished important proof against the hypothyroid pathogenesis of lymphoid nephrosis. It would seem that their work was not based on enough cases to warrant the conclusions that they draw.—L. M. Hurxthal.

The thyroid isthmus separated from the nervous system and remaining functional in rabbits (Isthme thyroïdien séparé du système nerveux et resté fonctionnel chez le Lapin). Champy, C. and E. Gley, Compt. rend. Soc. de biol. **102:** 898. 1929.

In young animals partial thyroidectomy was performed, leaving the isthmus in place but cutting all its nervous connections. The animals developed normally. After three to five months the animals were killed and serial sections of the isthmus made. No trace of nervous tissue to the parenchyma could be found. The tissue was otherwise normal.—J. C. D.

Chronic thyroiditis. Crane, W., California & West. Med. **35:** 443. 1931.

This brief paper is based upon 28 cases observed by the author. Chronic primary thyroiditis is a definite entity characterized by an inflammatory cellular infiltration of the gland with resultant massive fibrous tissue replacement of the acini. The clinical diagnosis is difficult, most cases being mistaken for those of malignant neoplasm. The procedure of choice is biopsy and division of the isthmus, or single resection, because of the marked tendency toward myxedema following classical double resection of the gland.—I. B.

Myxedema with associated primary type of anemia. Davis, Clara L., Pennsylvania M. J., **34:** 873. 1931.

The case described occurred in an unmarried white woman of 63, who was told in Ireland many years ago that she had myxedema. Since her arrival in this country, she had been in and out of hospitals many times for this condition. During the third admission to the hospital, she ran a slowly downward course to a fatal result in February, 1929. A study of the case while in the hospital led to a diagnosis of myxedema associated with pernicious anemia.—I. B.

Influence of the thyroid on edema caused by perfusion with salt solutions (Influence de la thyroïde sur l'oedeme par perfusion avec solution salines). Ferrari, R., Arch. ital. de biol. **85:** 208. 1931. Abst., Chem. Absts. **25:** 5705.

Perfusion of the ear or of the hind limb of the rabbit with oxygenated Ringer solution produces an edema of practically constant intensity, which, however, is very greatly increased in thyroidectomized animals. The addition of small amounts of thyroxine to the perfusion fluid reduces the edema to the same intensity as is found in the normal rabbit. The hydrophilia of the tissues, according to Aldrich and McClure's standard, is much greater in the thyroidectomized animals, which supports the view of the anti-edema function of the thyroid.

Qualitative and quantitative action of synthetic thyroxin on the metamorphosis of anurian larvae (Mode d'action qualitative et quantitative de la thyroxine synthétique. Son influence sur la métamorphose des larves d'anoures). Fontes, G. and M. Aron, Compt. rend. Soc. de biol. **102:** 679. 1929.

Synthetic thyroxin accelerates metamorphosis. The results are quantitatively related to the dose until a maximum is reached above which the speed of metamorphosis remains the same.—J. C. D.

Experimental regeneration of the thyroid parenchyma (Régénération expérimentale du parenchyme thyroïdien). Florentin, P. and M. Grujic, Compt. rend. Soc. de biol. **102:** 849. 1929.

Eserine salicylate injected into guinea pigs results in signs of secretory activity in the cytoplasm and nuclei of the aciner cells. The islets of non-aciner thyroid cells do not react nor do the parathyroids.—J. C. D.

Iodine deficiency theory of goiter (Zur Jodmangeltheorie des Kropfes). Hellwig, C. A., Klin. Wchnschr. **41:** 1913. 1930.

The author reviews some of the more important papers on the relation of iodine deficiency to goiter. He then gives the results of his own experiments on rats (27 animals used) which indicate that animals even from goiter-free

regions may develop goiter if given water with an unusually high calcium content. Iodine-poor food and distilled water produced atrophy of the thyroid. Calcium-rich (2% $Ca Cl_2$ added to the diet) and iodine-poor food produced an epithelial hyperplasia of the thyroid. Calcium-rich-iodine-rich diet produced a diffuse colloid struma. Rats fed the unbalanced diets weighed from 132 to 158 gms.; the controls on a balanced mixed diet weighed 170 gms.—I. B.

Studies in the physiology of vitamins. XVII. The effect of thyroid administration upon the anorexia characteristic of lack of undifferentiated vitamin B. Himwich, H. E., W. Goldfarb and G. R. Cowgill, Am. J. Physiol. **99:** 689. 1932.

The time required for development of the anorexia characteristic of vitamin B deficiency, and the amount of food ingested during the period of voluntary food intake were determined in four dogs under "normal" or basal conditions and during experimental hyperthyroidism. It was found that during hyperthyroidism (1) anorexia appeared in from one-half to two-thirds of the time required during the control period; and (2) the quantity of food ingested voluntarily per day was correspondingly increased. The total caloric intakes for the two experimental periods were approximately the same. This suggests that a definite relationship exists between a given amount of vitamin B and the catabolism of a definite quantity of foodstuffs. The four animals successfully maintained their weights by voluntary ingestion of food only when receiving sufficient amount of vitamin B.—Authors' Summary.

Investigations on the transplantation of thyroid in the guinea pig (Recherches sur les transplantations thyroïdiennes chez le cobaye. Phénomènes précoces). Hinschberger, G., Compt. rend. Soc. de biol. **106:** 234. 1931.

In guinea pigs thyroid transplants show three phases of development. Up to three days there is central degeneration with the establishment of peripheral vascularization. During the next four days vascularization is completed, but the graft fails to show signs of activity when the animal is injected with anterior lobe hypophysis extract. After a week the graft does respond to such injections. It is suggested that the establishment of nervous as well as vascular connections is essential before this response is possible.—J. C. D.

Demonstration in the blood of pregnant women of a substance increasing basal metabolism (thyroid gland hormone) (Nachweis einer grundumsatzsteigernden Substanz [Schilddrüsenhormon] im Blute von Schwangeren). Hoffmann, F. and K. J. Anselmino, Arch. f. Gynäk. **145:** 104. 1931. Abst., Chem. Absts. **25:** 5698.

A substance has been demonstrated in the blood of pregnant women which on injection of the serum into rats increases the basal metabolism. This substance is not present in the blood of non-pregnant women. The substance is present from the 3rd or 4th month of pregnancy on, increases during the course of pregnancy and falls rapidly during the puerperium. It is not present in the fetal blood. This substance increasing basal metabolism has been identified as the hormone of the thyroid gland. One cc. of the serum of a pregnant woman towards the end of pregnancy has the same effect on the basal metabolism in rats as 8-12 grains of thyroxine.

Specific dynamic action in Graves' disease (Über die spezifischdynamische Nahrungswirkung beim Morbus Basedow). Klein, W., Ztschr. f. d. ges. exper. Med. **75:** 842. 1931. Abst., Physiol. Absts. **16:** 559.

Eleven subjects of Graves' disease and 11 normals were compared as to their response to a test meal of 150 to 200 grams of meat (cooked with butter) and 80 grams of bread. Respiratory metabolism was determined by Benedict's or Knipping's apparatus at intervals of 1 to 1½ hours after the meal until resting values were returned to, usually 4 to 7 hours after the meal. The maximum rise in calories was almost always found to occur within 3 hours after the meal, in both the normals and the thyroid patients. The increase in calories in the normals was 15 to 31% over the basal value and in the hyperthyroid cases 6 to 20%—i.e., on the whole lower in the latter. A greater than normal specific dynamic action was only found in 2 cases of hy-

perthyroidism (thyrotoxic cases). Treatment with x-rays seemed more beneficial in cases with lower specific dynamic action than in those with values over the normal.

Blood changes in experimental hypo- and hyperthyroidism (rabbit). Kunde, M. M., M. F. Greene and G. Burns, Am. J. Physiol. **99**: 469. 1932.

The anemia of hypothyroidism (rabbit) is characterized by a greater than normal diameter of the erythrocytes; a color index greater than 1; a normal HCl content of the gastric contents; and a bone marrow which does not simulate either grossly or microscopically the bone marrow of pernicious anemia. The cholesterol content of the blood, accompanying the anemia of hypothyroidism, is greater than normal. Experimental hyperthyroidism in the rabbit causes an initial polycythemia and a corresponding increase in hemoglobin. Prolonged hyperthyroidism results in an anemia characterized by a color index less than one and a decreased diameter of the red blood cell. The total blood volume in experimental hypo- and hyperthyroidism (dye method) does not change beyond the limits of normal variation. In the normal adult rabbit, desiccated thyroids in dosages of 250 to 450 mgm. per day per rabbit, does not cause an appreciable increase in the per cent of reticulocytes. In the cretin a reticulocyte response varying from 4 to 10% occurs as the result of thyroid feeding.—Authors' Summary.

Gastric secretion in exophthalmic goiter and myxoedema. Lerman, J. and J. H. Means, J. Clin. Investigation, **11**: 167. 1932.

The attempt has been made to obtain knowledge of the gastric secretion in exophthalmic goiter and myxoedema, using histamine as the main secretory stimulus. A total of 50 patients with exophthalmic goiter and 17 patients with myxoedema were studied. The results obtained were compared with those of 200 normal people studied by the same method. The incidence of anacidity in exophthalmic goiter is 28% as compared to 13% for normal people. The figures corrected for age distribution become 45.6% and 12.6%, respectively. The incidence of hypoacidity is higher in exophthalmic goiter than in the normal, whereas hyperacidity is much lower. In general, normal people secrete twice as much acid in the stomach as patients with exophthalmic goiter, the actual values being 40.4 cc. and 21.0 cc., respectively. There is no correlation between the free acidity in exophthalmic goiter and the factors of age, red blood cell count, hemoglobin content, and basal metabolic rate. On the other hand, the incidence of anacidity shows a direct relationship to age and basal metabolic rate, and an indirect one to red blood cell count and hemoglobin content. The incidence of anacidity in myxoedema is 53%, but corrected for age distribution the figure becomes 75%, as compared to 15% for normal people of the same age range. There is no correlation between age and gastric acidity in myxoedema. There is a tendency to anemia in the patient with anacidity. It is suggested that the achlorhydria of exophthalmic goiter and myxoedema persists after treatment of the original condition. The cause of achlorhydria is unknown. Depression of a previously normal acidity will by itself not account for the high incidence of achlorhydria. The possibility of a threshold phenomenon is suggested, i.e., depression of the gastric secretion occurs up to a point, beyond which anacidity results.—J. Lerman.

Iodine content of the air, soil, water and food in a region of endemic goiter (Teneur en iodé de l'air, du sol, de l'eau et des aliments dans une région a goitre endémique).

The quantity of iodine eaten daily by the inhabitants of Salta (Quantité d'iode ingérée journellement par les habitants de Salta).

Iodine content in sheep thyroids in the province of Salta and along the seacoast (Teneur en iode des thyroïdes de moutons de la province de Salta et du littoral). Mazzocco, P. and C. Arias-Aranda, Compt. rend. Soc. de biol. **102**: 867; 869; 870. 1929.

In the Argentine province of Salta, the natural surroundings are poor in iodine and the iodine intake of the inhabitants is low. The sheep glands vary much in size, the larger glands being poorer in iodine. This is in contrast with those from the seacoast, where the iodine yield per gram is constant, regardless of the size of the gland.—J. C. D.

Place and manner of thyroxin action (Über Art und Ort der Thyroxinwirkung). Meyer, H. H., Arch. internat. de pharmacodyn. et de therapie, **8**: 1. 1930. Abst., Endokrinologie, **8**: 438.

The author discusses the question whether the outstanding changes in the metabolism and the irritability of the vegetative nervous system caused by the action of thyroxin can be traced to a single starting place in the central nervous system. Thyroxin has a direct peripheral action on the one hand and on the other hand, the author believes that the clinical pictures due to hyperthyroidism (increased basal metabolism, cachexia, and heart derangements) are exclusively conditioned by the central nervous system. This conception of thyroxin action is based on Enderlen's and Bohnenkamp's work on dogs. In these dogs the nerve fibers to the heart had been separated by cutting the vagus and extirpating the stellate ganglia. Despite a long period of thyroid material feeding no Basedowian symptoms could be noted, whereas in normal dogs under similar feeding, hyperthyroidism was noted. The author believes that these results indicate the fact that the action of thyroxin on metabolism and the heart depends upon central stimulation. He refers to articles in the literature supporting this assumption and postulates the theory of a sympathetic metabolic center in the brain.—Translated by J. Gagnon.

Papilliferous tumors of the thyroid gland and of aberrant thyroid tissue. Moritz, A. R. and F. Bayless, Am. J. Path. **7**: 675; 689. 1931.

Selecting 28 papilliferous tumors of the thyroid or of aberrant thyroid from the records of the Institute of Pathology of Western Reserve University, and 74 case reports from other sources, the authors classified them as cystadenomas, cystadenocarcinomas, adenomas, malignant adenomas and "carcinoids." The differential characteristics of each tumor were studied, including origin, pathogenesis, gross structure, microscopic structure and malignancy. Of the 102 tumors, 37 (37%) originated in aberrant thyroid tissue. It was apparent that the papilliferous character of adenomas and malignant adenomas did not distinguish them from the non-papilliferous forms so far as growth was concerned, being malignant only in the presence of demonstrable vascular or capsular invasion or metastases. The papilliferous structure was almost always microscopic. The papilliferous structure of the cystadenomas and cystadenocarcinomas was usually macroscopic. These tumors were seen to form a group that grew slowly and evidenced malignancy only by capsular invasion and metastasis to neighboring lymph nodes. More than half of them originated in aberrant thyroid tissue. Four cases of a condition termed "carcinoid" were reported. These were focal areas of atypical papilliferous acinar hyperplasia, superficially resembling scirrhous carcinoma, but which were not malignant and which originated only in non-tumorous thyroid glands.—F. Bayless.

The origin of the "parafollicular" cell, a second epithelial component of the thyroid gland of the dog. Nonidez, J. F., Am. J. Anat. **49**: (No. 3). 1932.

In the thyroids of puppies, stained with the silver-nitrate method of Cajal, a second epithelial component of the gland has been identified. It is represented by numerous cells arising from the follicular epithelium. Some of the follicular cells become very large, and argyrophile granules appear in their cytoplasm. The granule-laden elements (parafollicular cells) withdraw from the epithelium, singly or in groups, and form loose clusters in the interfollicular spaces. The argyrophile granules are slowly dissolved in the cytoplasm of the parafollicular cells, which do not degenerate but remain in good condition for a long time, perhaps throughout life. The nature of the argyrophile granules and the probable mechanism of the separation of the parafollicular cells from the follicular epithelium are discussed. By a process of elimination of other cell structures the conclusion is reached that the argyrophile granules probably represent the antecedent of a secretion poured into the blood stream through the capillary walls. No loss of colloid occurs during the separation of the parafollicular cells from the follicle wall, the adjoining cells spreading to fill the gap left by the migrating elements. However, some fluid may escape from the follicles. The possible rôle of the parafollicular cells is indicated.
—Author's Abst.

The Golgi apparatus in the thyroid cells in Basedow's goiter (Appareil de Golgi des cellules thyroidiennes dans le goitre basedowien). Okkels, H., Compt. rend. Soc. de biol. **106**: 305. 1931.

Fifty human goiters were examined, 25 of which were from cases of Basedow's disease. These latter show an increase in size and complexity of ramification in the Golgi apparatus. Inversion was not a constant feature.—J. C. D.

Cardiac features of goiter. Pemberton, J. deJ. and F. A. Willius, Proceedings Society Southern Surgical Association, J. A. M. A. **98**: 426. 1932.

In cases of hyperthyroidism, the clinical signs involving the circulatory system, such as tachycardia, palpitation, increase in pulse pressure, the tendency to flushing and sweating, basal cardiac murmurs, and occasionally the occurrence of bruits in the peripheral arteries, are well explained by an increase in the rate of circulation, which is a usual accompaniment of increases in basal metabolic rate. Although there are no distinctive histopathologic changes in the heart of patients who die in the active stage of hyperthyroidism, numerous instances of cardiac hypertrophy have been demonstrated by necropsy (15%); increases have been noted of from 100 to 200 gm. beyond the accepted standard of Smith, based on age, height and weight in cases in which primary cardiac disease was absent. Auricular fibrillation, the most common disorder of rhythm, occurs in about one-fourth of the cases of exophthalmic goiter and hyperfunctioning adenomatous goiter. The occurrence of congestive heart failure solely as a result of hyperthyroidism, even though its occurrence is infrequent, has been proved many times by careful correlations of clinical data and results of necropsy. In the preparation of patients for operation, caution in the use of digitalis is stressed. A study was made of 100 consecutive cases of congestive heart failure accompanying exophthalmic goiter and 100 consecutive cases of hyperfunctioning adenomatous goiter. The debility of the patient, commonly proportionate to the duration of hyperthyroidism, the degree of hepatic injury and the basal metabolic rate are more accurate indications of the operability than the severity of the cardiac disorder. A large percentage of the patients with congestive heart failure, who without operation are apparently doomed to an existence of chronic invalidism, will easily withstand partial thyroidectomy, subsequently regain complete cardiac efficiency, and enjoy many years of active and useful life.

The influence of the thyroid-parathyroid system and of the sympathetic nervous system on the blood-serum calcium. Speranska-Stepanova, E. N., Arkh. biol. Nauk. **30**: 593. 1930. Abst., Chem. Absts. **25**: 4605.

The experiments were carried out on cats under urethan anesthesia. Decerebration caused a brief increase in the serum Ca if the thyroid circulation was left intact. Strong cerebral irritation with simultaneous exclusion of thyroid circulation produced an increase in the serum Ca. Stimulation of the cranial end of the sympathetic trunk below the thyroid induces a rise in the Ca with the thyroid system left intact. The complete removal of the thyroid-parathyroid system or its exclusion from the general circulation may produce an increased Ca for several hours. A similar rise is produced by stimulation of the caudal endings of the abdominal sympathetic branches below the splanchnic nerves.

Roentgen rays and radium in toxic goiter and hyperthyroidism. Stevens, J. J., J. A. M. A. **97**: 1689. 1931. Abst., A. M. A.

In a discussion of the clinical course of toxic goiter and hyperthyroidism following treatment with roentgen rays and radium, the author calls attention to the fact that occasionally the patients suffer with increased toxicity for a few days following the initial treatments. Fortunately this is soon followed by relief, and gradual improvement takes place. Nausea, vomiting and diarrhea, when present, are among the first symptoms to improve or disappear. Early during the course of active treatment the strength begins to improve and pruritus disappears. Soon the weight increases, while palpitation, tachycardia, tremor, dyspnea and the tumor decrease and finally disappear. At this time the basal metabolic rate will generally be found to be within normal limits. The eye symptoms are among the last to disappear, and in some cases the ex-

ophthalmos never completely disappears. This is also true in cases treated surgically. In patients who have had severe thyroid intoxication for months or years, myocarditis frequently develops. In these cases the pulse rate is lowered but may never return to a perfect normal, no matter what the method of treatment, whether radiologic or surgical. If toxic goiter is superimposed on simple goiter, cystic goiter and other forms, the original tumor remains after treatment, and the enlargement of the gland appearing at the time of the development of toxicity disappears. In hyperthyroidism, i.e., thyroid intoxication without enlargement of the thyroid gland, superimposed on simple goiter, cystic goiter and other forms, treatment is not followed by any reduction in the size of the primary tumor. Correctly applied radiation therapy is second to no other method of treatment, and may be expected to cure from 85 to 90% of persons with toxic goiter and hyperthyroidism.

The relation of thyroid activity to the production of gastric ulcer by bile salts. Tashiro, S. and L. H. Schmidt, Med. Bulletin, Univ. Cincinnati, **6**: 137. 1931.

The dose of bile salt required to produce ulcer in a normal male guinea pig is 0.02 gm. per unit weight. Upon feeding of as little as 0.4 mgm. of thyroxin in two doses the ulcer producing dose of bile salts is lowered to 0.011 gm. per unit weight. The loss of weight following the feeding of thyroxin may be used as a general index to the susceptibility of an animal to the toxic action of the bile salts. A loss in weight due to fasting does not reduce an animal's resistance to bile salts action. Female animals are much more refractory to the actions of thyroxin and bile salt treatment than are male animals. An ulcer very similar to the acute human gastric ulcer may be produced by prolonged bile salt and thyroid treatment. The treatment of an animal with thyroxin is believed to increase the susceptibility of the animal to ulcer production by causing a reduction in the phospholipids of the tissues. This reduction must be the result of increased general lipid metabolism. There is a distinct possibility that clinical gastric ulcer is due to a disturbance in lipid metabolism.—Authors' Summary.

Fallacies and dangers in the treatment of exophthalmic goiter by iodine. Thompson, W. O. and Phebe K. Thompson, Ann. Int. Med. **5**: 1129. 1932.

Since the introduction of iodine the mortality from thyroidectomy for exophthalmic goiter in the leading clinics, has been lowered from about 1 to 4% to about 0.25 to 0.7%. This reduction is, we believe, less than is generally appreciated. The actual clinical improvement and reduction in basal metabolism caused by iodine is also somewhat less than is generally appreciated, owing to the fact that the influence of rest is usually not controlled. In very severe cases of the disease operation should be performed as soon as the metabolism reaches a level during the administration of iodine, because the beneficial effects in such cases may be of short duration. In cases in which the basal metabolism is high after the prolonged administration of iodine and those in which the basal metabolism is rising rapidly during the administration of iodine, no operative procedures should be undertaken until iodine has been omitted long enough for the refractoriness to it to disappear (usually about four weeks), and then readministered. In the routine preoperative treatment of exophthalmic goiter it is desirable to give suddenly an adequate excess of iodine and not to precede this with small doses. A few patients still die from typical postoperative thyroid crises in spite of the administration of large doses of iodine. These reactions sometimes occur in patients who have shown satisfactory responses to iodine before operation.—Authors' Summary.

Agglutination of colon bacilli from goiter cases by serum from goiter patients (Agglutination par le sérum de goitreux du colibacille isolé de l'intestin des goitreux). Turcu, T., Compt. rend. Soc. de biol. **107**: 381. 1931.

Several strains of colon bacillus were isolated from goiter cases and grown for two years. When these were tested with sera from normal and goitrous individuals no agglutination occurred with normal sera. Sixty-two per cent of the sera from the thyroid cases did agglutinate. This is further evidence of a bacterial factor in goiter.—J. C. D.

Studies on the normal thyroid in Rio de Janeiro (Etudes sur la thyroïde normale à Rio de Janeiro). Villela, G., G. and A. Penna de Azevedo, Compt. rend. Soc. de biol. **107**: 182. 1931.

In 22 individuals the average weight of the thyroid was 20.99 grams for the males and 15.53 grams for the females. The iodin averaged 8.37 mgm. per gram of dried gland.—J. C. D.

The Golgi apparatus and its position in the case of experimentally produced overactivity of the thyroid (L'appareil réticulaire de Golgi et sa position dans le cas de l'hyperactivité thyroïdienne expérimentalement provoquée). Wagschal, L., Compt. rend. Soc. de biol. **107**: 1015. 1931.

Guinea pigs' thyroids were overstimulated with hypophyseal extract. The Golgi net was invariably next the nucleus on the side toward the lumen of the acinus; that is, toward the facet of the cell where absorption was taking place and away from the secreting surface.—J. C. D.

The thyroid and the genital tract (Thyroïde et tractus génital). Watrin, J. and P. Florentin, Compt. rend. Soc. de biol. **107**: 51. 1931.

In young female guinea pigs implantation of thyroid fragments results in a marked increase in mitotic activity of the follicular cells of the ovary. —J. C. D.

Annual Index

Authors

Aaron, A. H.: cf. Hartman..... 43

Abbott, A. C. (Ball): Pathology of the thyroid gland of the human fetus and the new-born infant....331

Abbott, A. J. (Van Buskirk): The blood sugar response to epinephrin in thyroid-fed animals.....565

Abderhalden, E. (Buadze): The occurrence of the Abderhalden reaction after parenteral administration of the hypophysis preparation prehormone and of the ovarian hormone follicular 93

Abelin, I.: Effect of diiodotyrosine on the hyperthyroid metabolism..220

Abelin, I. (Jord): Ketonuria in experimental hyperthyroidism.....702

— (Spichtin): Influence of thyroid gland substances on the total creatinine content of the liver and muscle 220

Abelous, J. E. (Argaud): Appearance of a medullary reaction in the cortical substance of an abscessed adrenal 675

Adamberg, L.: Endocrine function of ovarian homoio-grafts and the fundamental laws of ovarian dynamics 205

Allardyce, W. J.: Studies on the chemistry and the physiology of the parathyroid hormone 218

Allan, F. N. (Scherer): Insulin allergy 417

Allan, H.: cf. Dodds..... 86

Allen, E.: Endocrine activity of ovary 570

Alessandri, H.: Studies on the hypotensive action of insulin-free pancreatic extracts 447

Altamirano, J.: cf. Cruz-Coke.....444

Alonza, L.: Influence of roentgen irradiation of thyroid on deaminizing functions of liver in exophthalmic goiter 702

Anselmino, K. J. (Hoffmann): Demonstration of an anti-glycogen substance (thyroid hormone) in the blood of pregnant women.....220

Anselmino, K. J. (Hoffmann): The demonstration of the hormone of the thyroid gland in the blood of pregnant women and the influence of the heightened function of the thyroid gland on metabolism, circulation and nervous excitability in pregnancy 702

Anselmino, K. J. (Hoffman): The relationship of the increased content of the blood of posterior lobe pituitary hormone to the existence of nephropathy and eclampsia in pregnancy 576

— cf. Hoffman 317, 706

Argaud, R.: cf. Abelous.....675

Arias—Aranda C.: cf. Mazzocco....707

Arnaudet, A.: cf. Blanchetiere..... 77

Aron, E.: Influence of ischemia on the evolution of the elements in the mammalian testis. Transformation of Sertoli cells into cells of the interstitial type 679

Aron, M.: Action of the anterior lobe of the hypophysis on the guinea pig ovary 577

— Biological methods for diagnosing over- and under-activity of the anterior lobe of the hypohysis in man 443

— Changes according to age in the thyroid in mammals 331

— Effect of the anterior lobe of the hypophysis on the thyroid in guinea pigs 686

— Physiologic significance of the ovary stimulating hormone associated with extracts of the anterior lobe of the hypophysis.443

— Studies on the indications of the activity of the anterior lobe of the hypophysis according to age and species, by physiologic measurement of the hormone in the body fluids and the agreement of this with the evidence of morphologic activity in the thyroid 312

— The action of the anterior pituitary upon the secretory activity of the thyroid.....565

— The distinction between the hormone which stimulates the thyroid and the substance which stimulates the ovary as found in extracts of the anterior lobe of the hypophysis.....685

— The specificity of the excito-secretory principle for the thyroid contained in extracts of the anterior lobe of the hypophysis...313

— (Dobrzaniecki): Effect of removal of the cervical sympathetic on thyroid function 331

Aron, M. (Van Caulaert and Stahl): Balance between the hormone of the anterior lobe of the hypophysis and of the thyroid within the body under normal and pathologic conditions 577
— cf. Dobrzaniecki 332
— cf. Fontes 705
— cf. Van Caulaert 695
Arnovljevitch, V.: The relations between the sugar and glutathione in the blood of normal and diabetic individuals 587
Arthus, A.: Complete thyroparathyroidectomy and cardiac-moderation 450
— (Jedrzejowska): Parathyroidectomy and vitamin D 450, 700
Artundo, A.: Basal metabolism in hypophysectomized dogs. Specific dynamic action in hypophysectomized dogs 686
— (Mazzocco): Action of the anterior lobe of the hypophysis on the respiratory exchange and the glycogen in white rats.....443
Asher, L. (Klein): Effect of adrenal cortex extract on the development of the testes 199
— (Ratti): Studies on the physiology of glands. CXX. The growth-regulating function of the thymus gland 220
Ask-Upmark, E.: A study of the parathyroid enlargement in osteitis fibrosa genalisata 327
— Parathyroid gland and calcium metabolism 700
— Thyreotoxicosis and tetany.....369
Askey, J. M. (Toland): Blood pressure and goiter 103
Atwell, W. J.: An experimental analysis of certain pituitary-adrenal-gonad relationship 639
— Functional relations of the hypophysis and the brain 242
Aub, J. C.: Critique of endocrine therapy 597

Bacq, Z. M.: cf. Cannon.....439
Baker, S. L.: Transplantation of a teratomatous ovarian tumor in the fowl: Production of a sex hormone by the cells of the transplants 679
Balint, J.: cf. Reiss.....96, 321
Ball, F. E.: Thyrotoxicosis with a normal metabolism early in the course of the disease 703
Ball, H. A.: Autopsy observations on one hundred and sixteen cases of malignant disease, in eighty-nine of which experimental injections of suprarenal cortex were given 559
Ball, R. G. (Greene, Camp and Rowntree): Calcification in tuberculosis of suprarenal glands: roentgenographic study in Addison's disease 559
— cf. Rowntree 300
Ball, R. P.: cf. Abbott.....331
Ballif, L.: cf. Parhon.....91, 212
Barborka, C. J.: Obesity 82
Bard, P.: cf. Lundstrom.....691
Barlow, O. W.: The action of insulin on the perfused frog heart and on the isolated rabbit intestine..214
— (Vigor and Peck): The action of insulin on the frog; influence of dosage, temperature, excision of liver, administration of glucose, sodium bicarbonate and calcium gluconate on reaction of frog to insulin 447
Barnes, B. O. (Carlson and Riskin): Studies on thyroglobulin. I. The digestibility of thyroglobulin 450
— cf. Juhn 333
Barr, D. P.: cf. Behrens.....120
Barral, P. (Roux); Is insulin itself a specific antigen?.....587
Bartlett, W. (Bartlett): An original method of estimating the thyrotoxic states 331
Bartlett, W., Jr.: cf. Bartlett.....331
Bastenie, P.: Origin of Hassall's corpuscles in the pathologic human thymus 591
Baumann, T.: Etiology and clinical aspects of acute suprarenal insufficiency. (Hemorrhages and hypoplasia of suprarenals) 675
Bayless, F.: cf. Moritz.....708
Beau, A.: Endocrines and coxa vara of adolescents 565
Behrens, L. H. (Barr): Alton Giant; hyperpituitarism beginning in infancy 120
Beilby, G. (Carlton): Exophthalmic goiter in children 221
Benetato, G.: The mechanism of the hyperglycemia produced by extracts of the posterior lobe of the hypohysis 313
— cf. Nitzescu 212
Bengtson, B. N.: Pituitary therapy of alopecia. A preliminary report.313
Benhamou, E. (Gilla): The increase of amino acids in the blood after adrenalin in normal individuals..675
Bernard, A. T.: cf. Ionesco.....697
Bernheim, M.: cf. Mouriquand.....701
Bennati, D. (Gautrelet and Halpern): The effect of hypotension on the secretion of an adrenal grafted into the neck.....437
Bennett, C. L.: Pubertas praecox in a girl of four: An attempt to estimate the follicular and anterior Pituitary sex hormones 529

Benoit, J.: Injections of testicular extracts in capons. Quantitative effect of the male hormone on the growth of the comb.....303
— Unilateral castration and compensatory hypertrophy of the remaining testicle in cocks and ducks 440
Berblinger, W.: cf. Zondek.....586
Berchtold, F.: cf. Stockinger.....585
Berg, B. N.: A study of the islands of Langerhans in vivo with observations on the circulation 587
Berkow, S. G.: Culpability of the suprarenals in the sypmtoms and late death from extensive superficial burns 297
Berliand, N. (Rywkin and Ssacharoff): Clinical anatomical biological parallels in Basedow's disease 332
Berman, L.: Endocrine treatment of Paget's disease 109
Bernard, L.: cf. Weiss 591
Bernhard, F.: The appearance of diabetes mellitus after acute pancreatic disease 214
Bernhardt, H.: Influence of hypophysis upon metabolism 208
Bertram, F. (Horwitz and Wahncau): Experimental and clinical investigation on the treatment of diabetes with insulin by mouth. IV. Liver extract as protector of insulin 587
Beutel, A.: cf. Mahler 329
von Beznak, A.: The amount of physiological diffusible calcium in serum of normal and parathyroprivic dogs 703
— The condition of the calcium in the blood serum of normal and parathyroprivic dogs 703
— The effect of parathyroidectomy on the sedimentation rate of the red blood corpuscles 703
Biasotti, A.: cf. Houssay.....95, 211, 317, 326, 678, 690
Bier, A.: The iodine metabolism in Basedow's disease and the explanation of the post-operative reaction following thyroidectomy.....221
Billmann, C.: Iodine content of blood, especially in exophthalmic goiter 704
Binet, L.: cf. Blanchetiere..... 77
Binswanger, H. F.: cf. Soskin.....328
Bisceglie, V.: The effects of hyperhormonization with follicular liquids on hypophysis, thyroid and suprarenals 302
Bischoff, F. (Long): The depletion of muscle sugar by adrenalin. I..297
— — The posterior pituitary hormone in metabolism 313
Bissonnette, T. H.: Studies on the sexual cycle in birds. V. Effects of white light of different intensities upon the testis activities of the European starling (Sturmus vulgaris) 85
Blair, J. E.: cf. Jaffe.....590
Blanchetiere, A. (Binet and Arnaudet): Glutathione in the adrenal during gestation 77
Bland, P. B. (First and Roeder): A comparative study of the Aschheim-Zondek and Mazer-Hoffman tests for early pregnancy 679
Bleicher, M.: Vascularization of the human adrenal 437
— cf. Lucien 299
Blöch, J.: Studies in the intermediary fat metabolism in diffuse parenchymatous lesions of the liver, under the influence of insulin and carbohydrates 587
Blumgarten, A. S.: Low basal metabolic rates in constitutional asthenics without hypothyroidism..704
Bodansky, A.: cf. Jaffe.....590
Boe, J.: Iodine metabolism and excretion after intravenous administration of thyroxine 704
Boeters, H.: Hypophyseal hormone of anterior lobe (prolan) and the male gonad 314
Bokelmann, O. (Scheringer): A contribution to the understanding of the function of the thyroid gland and iodine metabolism in pregnancy 450
Boolemen, Germaine: cf. La Barre.588
Bollman, J. L. (Mann): Enteral administration of insulin to normal dogs 696
Bonciu, O.: cf. Lieure 701
Bonilla, E. (Moya): The value of the cholesterol determination in thyroid patients 704
Boothby, W. M.: cf. Kepler.....104
Bourg, R.: Action of aqueous extracts of human placenta on the genital tracts of young rats of both sexes 303
— A new method for the Aschheim-Zondek reaction: Biological and clinical study 578
— Changes in the ovary and genital tract of kittens produced by "gravidine." Changes in the testes and genital tract of kittens produced by "gravidine"..570
— Changes produced by "gravidine" in the genital tract of immature rats studied by vital staining with injections of trypan blue 571
— Comparative studies of prolonged injections of urine from pregnant women in irradiated and non-irradiated young male rats.680
— Effect of injections of urine from men and children on the genital tract 303

Bourg, R.: Effect of injections of urine from pregnant woman on immature castrated and irradiated male rats 680
— Histologic changes in the genital tract of castrated male rats following repeated injections of urine from pregnant women...570
— Modifications produced by gravadine in the pregnant and non-pregnant adult cat 571
Bowen, B. D.: cf. Hartman.....562
Brabant, H.: cf. Watron.....685
Braier, B.: Bacillus coli vaccine on nitrogen metabolism of hypophysectomized dogs 209
— Influence of adrenalin on nitrogenous metabolism and glycemia of hypophysectomized dogs....199
— Metabolism of nitrogen and sugar in fasting dogs after hypophysectomy 578
— Nitrogen output of hypophysectomized dogs on a meat diet...578
— Nitrogenous metabolism in specific dynamic action of hypophysectomized dogs 209
— Protein metabolism and fasting hypophysectomized dogs 208
— Protein minimum in hypophysectomized dogs 209
— The C/N ratio in hypophysectomized dogs on a diet lacking in vitamin B 314
Bram, I.: Physostigmine salicylate in the treatment of exophthalmic goiter. Observations in two hundred cases 221
— Quinine and iodine in exophthalmic goiter 157
— Relationship of quinine tolerance to thyroid secretion 592
Branion, H. D.: cf. Taylor 330
Braucher, Pela Fay: cf. Riddle....321
Briese, Marie: cf. Parhon.....309
Brieu, T. (Fuchs, Santenoise and Vidacovitch): Action of vagotonin on glycemia 696
— cf. Santenoise 698
Britton, S. W.: Evidence of chief function of adrenal cortex.....633
— Maternal and fetal blood sugar changes under various experimental conditions 324
— Observations on adrenalectomy in Marsupial hibernation and higher mammalian types 437
— (Flippin and Silvette): The oral administration of cortico-adrenal extract 560
— (Silvette): Observations on the cortico-adrenal hormone 77
— cf. Corey 560
Brogan, A. J.: cf. Lerman.....251
Brouha, de Adele: Notes on a hormonal test for pregnancy 304
Brouha, L. (Simonnet): Follicular maturation, corpora lutea and oestrous 686
— cf. Desclin 315
Brown, T. K.: cf. Soule 695
Browne, J. S. L.: cf. Collip..... 86
Brownell, K. A.: cf. Hartman.....
.....79, 298, 521
de Bruin, M.: Observations on metabolism of healthy children with a consideration of the specific dynamic action of food 209
Bryan, A. H. (Gaiser): The influence of diet and the anterior pituitary growth hormone on the growth rate of adolescent rats....686
Bryan, W. R. (Garrey): Contributory factors in parathyroid tetany in dogs; high temperature, panting and overventilation 219
Bryant, A. R.: The effect of total thyroidectomy on the structure of the pituitary gland in the rabbit..439
Buadze, S.: cf. Abderhalden..... 93
Bucciardi, G. (De Niederhäusern): The action of insulin on the muscle contraction of the frog.....214
Buchanan, J. A.: Site of action of iodine in goiter 65
Buchbinder, W. C.: Some cases of so-called "recurrent thyrotoxicosis" 592
Buchheim, W. (Zaleski): Sex hormones and the sympathetic nervous system 440
Buchwald, K. W. (Cori): The action of epinephrine and insulin in frogs under anaerobic conditions..566
— cf. Cori 199, 297, 560
Buckley, O. B.: The effect of subcutaneous injections of trypsin on the blood sugar and on insulin action 587
Burch, J. C. (Williams, Wolfe and Cunningham): Hypophyseal-ovarian relationship 578
— (Wolfe and Cunningham): Experiments on endometrial hyperplasia 541
Bürger, M. (Rückert): The formation of fat from carbohydrates under the influence of insulin 98
Burns, G.: cf. Kunde.....707
Burns, R. K., Jr.: The process of sex transformation in parabiotic amblystoma. II. Transformation from male to female 85
— (Buyse): Effects of hypophysectomy on the reproductive system of salamanders 578
— — The effects of extracts of the mammalian hypophysis upon immature salamanders 443
Busman, G. J.: Cutaneous diseases from the metabolic and endocrine aspect 678
Busquet, H.: Inhibition by heifer serum of the appearance of neutral characters in ovariectomized chickens 680

Butenandt, A.: Chemical investigation of the sex hormone 680
— The physical and chemical properties of the follicular hormone.571
— The preparation of pure follicular hormone from pregnancy..571
Buyse, A.: cf. Burns.....443, 578
Byron, C.: cf. Wishnofsky 100

Caffey, J.: cf. McLean.....438
Cahane, F.: cf. Cahane.....566
Cahane, M.: Changes in liver glycogen in gonadectomized animals.205
— Endocrine function of the pancreas and calcium metabolism.696
— (Cahane): The endocrine function of the salivary glands.....566
— cf. Parhon 219, 453
Calatroni, C. J.: cf. del Castillo.304, 440
Calder, R. M.: Pituitary cachexia (Simmond's disease) treated with anterior pituitary extract 686
Cameron, J. D. S. (Hill): Heart block in toxic goiter 592
Camp, J. D.: cf. Ball.....559
Candela, N.: Follicular, luteinic and mammarian incretotherapy and its influence on the genital tract and on the endocrine system. Experimental study 566
Cannon, W. B.: Studies on the conditions of activity in endocrine organs. XXVII. Evidence that medulliadrenal secretion is not continuous 437
— (Bacq and Moore): Studies on the conditions of activity in endocrine organs. XXVI. A hormone produced by sympathetic action on smooth muscle 439
— cf. Freeman 202
— cf. Rosenblueth 679
Cardini, C.: cf. del Castillo 214
Cardoso, D. M.: cf. Martins.....574
Caridroit, F. (Régnier): Moulting and castration in Rouen ducks...304
Carlson, A. J.: cf. Barnes.....450
Carmichael, H. T.: Squamous epithelial rests in the hypophysis cerebri 314
Carey, B. W.: cf. Trimble.....100
Carlson, A. J.: cf. Knude.....203
Carlton, J. G.: cf. Beilby.....221
Casey, W. R.: cf. Mowrer 431
del Castillo, E. B.: Ovarian grafts in male and female white rats...681
— (Cardini): Effect of insulin on the appearance of the sexual cycle in white rats 214
— (Calatroni): Ovarian grafts in unspayed rats 440
— — The periodic sex cycle and folliculin 304
Castle, W. B.: cf. Means.....105
Castrex, M. R. (Schteingart): Action of the hypertensive and ocytocic principles of the posterior lobe of the hypophysis on basal metabolism 315
Cattaneo, C.: Physiopathology of status thymo-lymphaticus 591
Cattell, M. (Edwards): Epinephrin action in relation to the hydrostatic pressure effect on the contraction of cardiac muscle.....199
Cattell, R. B.: Aberrant thyroid...451
Ceruti, G. (Sapegno): The action of insulin on thermoregulation 216
des Cespédes, C.: cf. La Barre.....697
Challans, Joanna S.: cf. Johnson...278
Chambers, W. H.: cf. Himwich..99, 216
Champy, C. (Gley): The thyroid isthmus separated from the nervous system and remaining functional in rabbits 705
Chang, H. C. (Chen): On the "sympathetic substances" obtained from the gut and other organs of the toad 560
Charipper, H. A.: cf. Haterius.....210
Chatagnon, P.: Effect of castration on the scent glands of the goat..571
Chiefitz, A. B.: Gynecomastia..... 93
Chen, Y. P.: cf. Chang.....560
Chesney, A. M.: cf. Webster.....107
Chiapponi, L.: cf. Montpellier.....568
— cf. Ribiere 310
Choi, M. H.: Homoiotransplantation of the amphibian thyroid anlage..592
Chudoroschewa: cf. Istanamowa...299
Cleveland, R. (Wolfe): A differential stain for the anterior lobe of the hypophysis 579
— cf. Wolfe 696
Clute, H. M.: Clinical aspects of thyroid malignancy 451
Coelho, E.: Thyroxin and the specific dynamic action of sugar.....332
— (Oliveira): Action of thyroxin on the sodium chloride equilibrium of the blood 451
— (Rocheta): Thyroxin and gastric acidity 221
Cole, W. H. (Womack and Ellett): The production of hyperplasia of the thyroid gland by chemical means, with special reference to purine bases and their derivatives.335
Collin, R.: Finer structure of the cells of the hypophysis 687
— Finer structure of the cells of the pituitary gland 687
— (Drouet, Watrin and Florentin): The effect of hypoglycemia on cellular activity of the anterior and posterior lobes of the hypophysis and the tuber cinereum. The effect of hypoglycemia on cellular activity of the thyroid, parathyroids, pancreas, salivary glands and thymus. The effect of hypoglycemia on cellular activity of the spleen and adrenals 566
Collins, W. S.: cf. Koster.....562
Collip, J. B. (Thomson, Browne, McPhail and Williamson): Placental hormone 86

Colombi, C.: The influence of the anterior pituitary hormone on the testicles of guinea pigs.....579
Columba, D.: Insulinemia in obesity and in emaciation 215
Comel, M.: On the relations between strontium and parathyroids.202
Condorelli, F.: Influence of acetylcholine on insulinemia 98
Conklin, C.: cf. McClendon..... 89
Cooley, T. B.: Hyperparathyroidism and similar diseases of bone.....222
Coombs, H. C. (Wortis and Pike): The effects of absinthe on the cat, following bilateral adrenalectomy.560
Cordier, R.: cf. Gerard.....298
Corey, E. L. (Britton): The induction of precocious sexual maturity by cortico-adrenal extract.....560
Cori, C. F. (Cori): Influence of epinephrine and insulin injections hexosephosphate content of muscle 561
— (Buchwald): Effect of continuous intravenous injection of epinephrine on the carbohydate metabolism, basal metabolism and vascular system of normal men.297
— The calorigenic action of epinephrine in frogs before and after hepatectomy 560
— cf. Cori.....199
— (Cori and Buchwald): The mechanism of epinephrine action; changes in liver-glycogen and blood lactic acid after injection of epinephrine and insulin.....199
— cf. Cori.....561
Corkhill, A. B. (Marks): The effect of adrenaline on muscle glycogen.199
Corner, G. W.: cf. Wilson.....576
— Hormonal control of lactation; non-effect of corpus luteum; positive action of extracts of hypophysis 304
Cosin, C. F.: cf. Hurst.....101
da Costa, A. C.: The relations between the cortical and medullary portion of the adrenals in mammals 299
Cottrell, J. E.: Dwarfism and infantilism 687
Courrier, R.: Do large doses of folliculin when injected have an effect on the Graafian follicle?.....
— Folliculin and the uterine changes preparatory to implantation of the egg.....304
— Studies on the antagonism of follicular and luteal hormones..... 86
— The female sex hormones.....571
— (Kehl): Further investigation on the action of folliculin in rabbits carrying corpora lutea.....572
Cowgill, G. R.: cf. Himwich.....706
Cowley, R. J.: The hypoglycemic action of the hypophysectomized dog's blood.....687
Crainiceanu, A.: cf. Daniel.....681
Crane, W.: Chronic thyroiditis.....705
Crile, G. W.: Recurrent hyperthyroidism, neuro-circulatory asthenia and peptic ulcer. Treatment by operation on the suprarenal sympathetic system.....561
Crisera, A.: cf. Racchuisa.....201
Cronin, H. J.: Psychiatric reactions from dysinsulinism in a diabetic..325
Cruickshand, Ethel M.: Factors affecting size and iodine content of the thyroid in fowls.....451
Cruz-Coke, E. (Altamirano): Action of extracts of the anterior lobe of the hypophysis on the chemistry of the liver.....444
Crosby, A. A.: cf. Hartman.....298
Cunningham, R. S.: cf. Burch..541, 578
Cushing, H.: The method of action of pituitrin introduced into the ventricle 687
— The reaction to posterior pituitary extract (pituitrin) when introduced into the cerebral ventricles 579
— The similarity in the response to posterior lobe extract (pituitrin) and to pilocarpine when injected into the cerebral ventricles....580
Cutting, R. A.: cf. Gage.....588

D'Amour, F.: cf. Ihrke.....441
D'Amour, F. E.: cf. Knude.....203
— cf. Spencer.....647, 684
Danelivskii, B. (Wyalkova): The effect of insulin on the sympathetic nervous system..... 98
Daniel, C. (Crainiceanu and Mavromati): Clinical effects of folliculin on the arterial pressure in man. Action of folliculin on arterial pressure after paralysis of the vagus 681
Darley, W.: cf. Draper.....444
Davis, Clara L.: Myxedema with associated primary type of anemia 705
Defauw, J.: Variations in glycogen content of the heart in animals with experimental hyperthyroidism 451
De Jong, H.: Hormonal experimental catatonia 440
Demoor, P. (Slosse): Treatment of goiter, accompanied by hyperthyroidism 592
De Niederhäusern, A.: cf. Bucciardi.214
Derevici, H.: cf. Parhon.....223, 595
Derevici, M.: cf. Parhon.....595
Desclin, L. (Brouha): Histological changes in the hypophysis of guinea pigs during pseudo pregnancy 315
Dessy, G.: Feeding experiments on tadpoles with endocrine glands taken from young and old cattle... 82
Di Benedetto, E.: Action of phloridzin on hypophysectomized toads...315
— Phlorizin in hypophysectomized toads 209

Dickens, F.: The preparation and properties of the gonad-stimulating hormone from the urine of pregnancy 205
Dietel-Heidelberg: Concerning the occurrence, mechanism and fate of the melanophore hormone in the warm-blooded organism 688
Dingemanse, E. (Freud, De Jongh and Laqueur): Concerning the presence of large amounts of female (sex) hormone menformen in the blood of cancer patients (males) 681
— (Freud, Kober, Laqueur and Münch): Purification of the male hormone by high-vacuum distillation 572
— (Freud, Kober, Laqueur, Luchs, Münch): Separation of the male sex hormone from the female hormone, menformone ...205
— (de Jongh): The sexual hormone of the pituitary. Action on female animals 580
Dobrzaniecki, W. (Aron): Effect of stimulation of the cervical sympathetic on thyroid function 332
— cf. Aron 331
Dock, W.: The relative increase in metabolism of the liver and of other tissues during protein metabolism in the rat..... 97
Dodds, E. C. (Greenwood, Allan and Gallimore): Properties of the comb growth promoting substance obtained from testes and urine.. 86
Dohrn, M.: cf. Schoeller.....684
Doisy, E. A. (Thayer): Preparation of theelol 681
Doisy, A.: cf. Thayer.....576
Donelson, E. (Hunscher and Macy): Metabolism of women during the reproductive cycle. IV. Calcium and phosphorous utilization in late lactation and during reproductive rest 304
Dorn, J. H. (Morse and Sugarman): Early pregnancy—a hormone test for its diagnosis 572
Drabkin, C.: cf. Schwarz 310
Dragstedt, C. A.: Ossification in the absence of the parathyroid glands 93
Dragstedt, L. R. (Ellis): The effect of diverting adrenal vein blood into the portal vein on blood sugar 77
Draper, W. B. (Darley and Harvay): The effect of pituitary extract upon the tonus of the human pelvis and ureter and its possible application in the therapeutics of plelitis and related conditions 444
Dreyfus, G.: cf. Labbe.....318
Drouet, P. L.: cf. Collin.....566
Durrant, E. P.: Relation of hysterectomy of long standing to voluntary activity in the white rat.... 86
— cf. Rosenfeld 684
Dubois, R.: cf. Lesne.....700
Dworkin, S.: Insulin and heart rate after sympathectomy and vagotomy 447
— The response of sympathectomized animals to insulin 215

Edmunds, C. W. (Smith): Experimental suprarenal exhaustion ... 78
Edwards, D. J.: cf. Cattell.....199
Ehrstrom, R.: Adiposogenital dystrophy, diabetes mellitus and albuminuria of neurogenic origin; two cases 444
Eidelsberg, J.: Endocrinopathies: thyro-pituitary syndromes; diagnosis and treatment 83
Eisenberg, A. A.: cf. Lazarus.....563
Elmer, A. W.: (Ptaszek): Comparative effect of vasopressin and pituitrin on intestinal peristalsis. Action of ocytocin on peristalsis and the antagonism between vasopressin and ocytocin 580
Fontaine, R. (Hermann): The mechanism for hyperglycemia following lumbar sympathectomy in dogs 567
Ellett, W. H.: cf. Cole.....335
Ellis, J. C.: cf. Dragstedt..... 77
Ellsworth, R.: Secondary alterations in total serum calcium after the administration of glucose and insulin 98
Emanuel, S.: Effects of intraperitoneal implantation of hypophyses from rats castrated before puberty 690
— Mode of action of hypophysis after castration, demonstrated by implantation experiments...315
— Note on the follicular hemorrhages in the Aschheim-Zondek reaction 93
Emmerson, M. A.: cf. Free..... 87
Enachesco, M.: cf. Ionesco.....697
Engelbach, W.: The growth hormone 1
Engle, E. T.: Action of extracts of anterior pituitary and of pregnancy urine on testes of immature rats and monkeys.....506
— Experimentally induced descent of testis in Macacus monkey by hormones from anterior pituitary and pregnancy urine.....513
Erhardt, K.: Hormonal analysis of blood and urine of non-pregnant women after transfusion of blood from pregnant donors 87
Escalier, A.: cf. Labbe.....318
Esch, P.: Hormone therapy with intramuscular injection of pregnancy blood in disturbances of menstruation 305
Ettinger, G. H. (Smith and McHenry): The diagnosis of pregnancy by the Aschheim-Zondek test 93
Eufinger, H. (Wiesbader): The Reid-Hunt reaction and pregnancy....206

von Euler, U. S.: Stimulating action exerted peripherally on cellular metabolism by adrenin. Antagonistic action of ergotamine..562
Evans, F. A.: The level of oxygen exchange in obesity as a factor in planning treatment 592
Evans, H. M. (Meyer and Simpson): Relation of Prolan to the anterior hypophyseal hormones 444
— (Simpson): Hormone of the anterior hypophysis 315
— (Swezy): Ovogenesis and the normal follicular cycle in adult mammalia 305
— cf. Reichert 445
Evans, W.: Case of myxedema with ascites and atony of the urinary bladder 409
Epstein, E. Z.: The influence of hypnotics and thyroxin on diuresis...452

Fabiao, M.: cf. Martins.....309
Fancher, J. K.: Some observations on anterior lobe hyperpituitarism.611
Farguharson, R. F.: cf. Graham.... 95
Fauvet, E.: Histological changes in the liver and kidneys after intoxication with extracts of the posterior lobe of the hypophysis.....580
Fedoroff, P. A.: Clinical course of hyperinsulinemia 325
Ferrari, R.: Influence of the thyroid on edema caused by perfusion with salt solutions 705
Ferreira de Mira, M. (Fontes): Muscular fatigue in rabbits surviving double adrenalectomy 562
Findley, R., Jr.: Failure of irradiated ergosterol to relieve parathyroid tetany 327
First, A.: cf. Bland.....679
Fitch, Alice: cf. du Vigneaud.....699
Flippin, J. C.: cf. Britton.....560
Florentin, P.: Experimental studies and the interpretation of the variations in the color reaction of the colloid in thyroid glands.....593
— Persistence of an embryonic structure in the thyroid of the adult hedge hog 452
— (Grujic): Cytological studies on the guinea pig thyroid 332
— — Experimental regeneration of the thyroid parenchyma 705
— cf. Collin 566
— cf. Watrin 685, 711
Fluhmann, C. F.: Hyperplasia of the endometrium and the hormones of the anterior hypophysis and the ovaries 94
— Hyperplasia of the endometrium and the hormones of the anterior hypophysis and the ovaries.581
— (Morse): Studies on uterine hemorrhage; relation of hemorrhage to events of menstrual cycle and to pathologic findings.306
Foglia, V. G.: Action of drugs on internal secretion of pancreas.....325
Foncin, Mme. R.: Effect of repeated injections of urine from pregnant women on experimental cryptorchid testes in guinea pigs.....307
— Experimental cryptorchidism in immature guinea pigs. Early effects 306
Foncin, R.: Response of experimental cryptorchid testes of immature guinea pigs to repeated injections of urine from pregnant women...681
Fontes, G. (Aron): Qualitative and quantitative action of synthetic thyroxin 705
— (Thivolle): Effect of synthetic thyroxine on urinary carbon and nitrogen. Effect of thyroidectomy alone and associated with injections of thyroxin and the urinary carbon and nitrogen...333
Fontes, J.: cf. Ferreira de Mira....562
— cf. de Mira.....300, 438
Foramitti, C.: The fate of transplanted testicular parenchyma....682
Ford, F. A.: Treatment of Roentgen rays in ovarian dysfunction.....572
Frank, A. H.: cf. Turner..... 92
Frank, R. T.: Rôle of female sex hormone 572
Frattini, B. (Maino): Follicular hormone 307
— — Isolation of the male sexual hormone in crystal form, soluble in water..... 87
Freeman, N. E. (Phillips and Cannon): An unsuccessful attempt to demonstrate humoral action of "vagus substance" in the circulating blood 202
Frei, W. (Emmerson): The calcium content of the serum of cattle with reference to the influence of the sexual organs 87
Freud, J. (de Jongh, Laqueur and Münch): On the male hormone.. 87
— (de Jongh and Laqueur): The effect of the female hormone (Menform) on the plumage of the bird 682
— cf. Dingemanse 205, 572, 681
Frey, E. K. (Kraut and Schultz): A pancreatic circulatory hormone... 98
Friedman, M. H.: Further studies on the mechanism of ovulation... 88
— On the mechanism of ovulation in the rabbit. III. The rate of mechanically ruptured follicles.206
Friedman, J. L. (Nice): Multiple ovaries and the oestrous cycle in the white rat 307
Fuchs, G.: cf. Brieu.....696
— cf. Santenoise 698
Fullerton, C. W.: The cardiac output in hyperthyroidism 452

Gaebler, O. H.: Animal calorimetry. The specific dynamic action of meat in hypophysectomized dogs.210

Gage, I. M. (Ochsner and Cutting): Effect of insulin and glucose on normal and obstructed intestine..588
Gaiser, D. W.: cf. Bryan.....686
Gallant, I. W.: Hyperthyroidism...103
Gallimore, E. J.: cf. Dodds..... 86
Gammon, G. D. (Tenery): Hypoglycemia; the clinical syndrome, etiology and treatment; report of a case due to hyperinsulinism.....215
Gardiner-Hill, H. (Smith): Treatment of ovarian deficiency with ovarian extract (oestrin)..... 88
Gardner, W. U.: cf. Turner.....446
Garcin, R.: cf. Guillain.....316
Garrey, W. E.: cf. Bryan.....219
Gasteiger, H.: Rare ocular changes in thyroidal disturbances.....452
Gautrelet, J.: cf. Bennati.....437
Gavrila, I. (Milhaileanu): The action of the hypertensive principle (vasopressin) and the ocytocic principle (ocytocin) of the posterior lobe of the hypophysis on the blood sugar in man.....689
Gedroyc, M. (Kosowski): Red blood cells and the absorption of certain nutritional and hormonal substances, especially adrenin 297
Geelmuyden, H. C.: Some questions and problems of diabetes research including some evidence of a metabolic-physiological theory of diabetes mellitus 215
Geiger, E.: Mobilization of the muscle glycogen by adrenalin and the resynthesis of lactic acid in the liver 200
Gellerstedt, N. (Grill): A clinical and anatomic contribution to the knowledge of combined diabetes mellitus and insipidus; report of a case treated with insulin and salyrgan in which the patient died with symptoms of hypoglycemia..447
Gerard, P. (Cordier and Lison): On the nature of the chromaffin reaction 298
Gerschmann, R.: Calcium and phosphorus in plasma of hypophysectomized dogs 210
— The parathyroids and decreased blood calcium following fluorine.222
— Urinary elimination of phosphates and phenol in fasting hypophysectomized dogs 316
Gilbert-Dreyfus: Hyperthyroidism and its treatment 222
Gibert, S.: cf. Rathery 326
Gilla, R.: cf. Benhamon.....675
Giusti, L.: cf. Houssay....307, 689, 690
Gley, E.: cf. Champy 705
Globus, J. H.: cf. Strauss.....323
Gnagi, W. B.: cf. Womack.....218
Gold, E.: Effect of radiation in a case of pseudohermaphroditism with malignant adrenal cortical tumor 675
Goldburgh, H. L.: cf. Mohler 697
Goldfarb, W.: cf. Himwich.....706
Goldzieher, M. A.: Nodular hyperplasia of adrenal medulla in hypertension 20
— (Gordon): Syndrome of adrenal hemorrhage in new-born.....165
— (Kaldor): Experimental studies concerning the rôle of the hypophysis in water metabolism.. 94
— cf. Koster 562
Goormaghtigh, N. (Heymans): Parathyroid hypertrophy after denervation of the carotid sinus and the cardio aortic zone 327
Gordon, C.: cf. Hogben 95
Gordon, M. B.: cf. Goldzieher.....165
Gostimirović, D.: Pregnancy reaction in juvenile male mice from injection of urine containing the sex hormone from the anterior lobe of the hypophysis 316
— The "Prolan" output of carcinomatous women after radiation treatment 689
Gottesman, J. M. (Perla): Effect of injections of cortin on resistance of suprarenalectomized rats to large amounts of histamine..... 78
— — Immunological studies in relation to suprarenal gland. VII. Effect of bilateral suprarenalectomy on acquired resistance in rats 78
— cf. Perla 79, 80
Grabowski, W.: Roentgen therapy in menopause 682
Graham, D. A. L. (Farguharson): Cases of Simmond's disease 95
Graham, E. A.: cf. Womack.....218
Grant, Madeleine P.: Mechanism of colloid release from urodele thyroid during diagnostic stages of metamorphosis (Amblystoma jeffersonianum, Amblystoma opacum).103
Greenberg, D. M.: cf. Gunther.....328
Greene, C. H. (Rowntree, Swingle and Pfiffner): Metabolic studies in Addison's disease: The effect of treatment with cortical hormone of the suprarenal gland 675
— cf. Ball 559
— cf. Rowntree 300
Greene, C. W.: cf. Hartman.....562
Greene, M. F.: cf. Kunde.....707
Greenwood, A.: cf. Dodds..... 86
Grönlund, L.: cf. Räiha 698
Grueter, F.: cf. Stricker.....213
Gruhzit, O. M.: Gland extracts in experimental carcinoma and sarcoma of albino rats 302
Grujic, M.: cf. Florentin.....332, 705
Gruter, F.: Action of anterior pituitary extract on small laboratory and domestic animals 316
Guerriero, C.: Morphological study of the uterine horns during sexual repose in immature, adult and castrated rabbits. The structure of the epithelum of the uterine horn during the follicular and lutein stages of ovarian activity.....682

Guillain, G. (Lechelle and Garcin): Increase in number of blood cells associated with certain syndromes of hypophyseal and hypophyseal-tuber regions 316
Guisti, L.: cf. Houssay 203, 211
Gunther, L. (Greenberg): The diffusible calcium of the blood stream in tetany 328
Gustavson, R. G. (Van Dyke): Further observations on the pregnancy response of the uterus of the cat 206
— cf. Knude 203
— cf. Spencer 647, 684

von Haam, E. (Thatcher): Relation of adrenal glands to relative erythrocyte volume 666
Halpern, N.: cf. Bennati 437
Hannan, J. H.: Further observations on ovarian transplantation 307
Harris, R. H.: The Coffey-Humber extract of suprarenal cortex substance: A clinical study of four hundred and fifteen patients with malignant tumors who received experimental injections 298
Harris, Seale: Hyperinsulinism and dysinsulinism (Insulogenic hypoglycemia) 29
Harrow, R.: cf. Palmer.....701
Hartley, E. C.: The tetanoid syndrome in pregnancy 573
Hartman, C. G.: Phylogeny of menstruation 573
Hartman, F. (Brownell): The vital hormone of the adrenal cortex.... 79
Hartman, F. A. (Aaron): Cortin in Addison's disease 43
— (Bowen, Thorn and Greene): The vital hormone of the adrenal cortex 532
— (Brownell and Crosby): The relation of cortin to the maintenance of body temperature....298
— (Brownell and Lockwood): Studies indicating function of cortin...521
— (Thorn and Potter): Cortin in case of possible adrenal insufficiency during pregnancy 155
Hartman, G. C. (Squier): The follicle stimulating effect of pig anterior lobe on the monkey ovary. 95
Harvey, J. L.: cf. Draper.....444
Haterius, H. O. (Charipper): Experimental studies of the anterior pituitary. II. The occurrence of pregnancy cells in mice following continuous anterior-lobe administration 210
— (Nelson): Experimental studies of the anterior pituitary 689
Hauptstein, P.: Experimental and clinical studies concerning the action of hormones in gynecology.. 83
Haurowitz, F.: cf. Reiss..... 96
Hayes, F. W.: cf. Himwich.....210
Heller, R. E.: Cowper's gland and its reaction to castration and to different sex-hormone conditions.683
— Spontaneous activity in male rats in relation to testis hormone..626
Hellwig, C. A.: Iodine deficiency theory of goiter 705
— Iodine deficiency and goiter; influence of a diet poor in iodine on the thyroid gland in white rats 103
Helpler, Opal E.: cf. Simonds.....596
Herlant, M.: Effect of injections of urine from pregnant women on the genital tract of the hibernating male hedgehog. Effect of injections of urine from pregnant women on the genital tract of the hibernating female hedgehog.....683
Hermann, H.: cf. Tournade...565, 677
Hermann, L. G.: cf. Fontaine.....567
Herzfeld, E.: The influence of hypophyseal preparations and various proteins on the specific dynamic actions of proteins 316
Hess, A. F. (Smith): Excessive ultra-violet irradiation; effect on the nutrition and the endocrine glands of rats 567
Heymans, C.: cf. Goormaghtigh...327
Hill, I. G. W.: cf. Cameron.....592
Hill, M. (Parkes): On the relation between the anterior pituitary body and the gonads. II. The induction of ovulation in the anoestrous ferret 690
— — Relation between the anterior pituitary body and gonads. III. Fractionation and dilution of ovary-stimulating extracts 210
Hillmann, M. L.: Cholesteremia in certain diseases of endocrine glands 593
Himmelberger, L. R.: Thyroid hormone in blood and urine 264
Himwich, H. F. (Chambers, Koskoff and Nahum): Studies in carbohydrate metabolism. II. Glucose lactic acid cycle in diabetes.....99, 216
— (Goldfarb and Cowgill): Studies in the physiology of vitamins. XVII. The effect of thyroid administration upon the anorexia characteristic of lack of undifferentiated vitamin B 706
— (Hayes): Effects of posterior pituitary extracts on basal metabolism 210
— (Spiers): The effects of adrenalin, ephedrine, and insulin on blood fat 302
Hinchberger, G.: Investigations on the transplantation of thyroid in the guinea pig 706
Hisaw, F. L.: cf. Meyer 655
Hochrein, M. (Keller): The effect of adrenalin and substances related to adrenalin (sympathol and ephetonin) upon the circulation..437

Hockett, A. J.: cf. Thienes.....213
Hofbauer, J.: Relation of anterior lobe of the hypophysis to cancer of the uterus 211
Hoffmann, F. (Anselmino): Demonstration in the blood of pregnant women of a substance increasing basal metabolism 706
—— The demonstration of the antiduretic component of the hypophyseal posterior lobe hormone and a substance producing blood pressure in the blood of nephropathic and eclamptic individuals...317
— cf. Anselmino.....220, 576, 702
Hoffman, J.: The effect of anterior hypophyseal implants upon senile ovaries of mice 445
Hogben, L. (Gordon): Studies on the pituitary. VII. The separate identity of the pressor and melanophore principles 95
— (Slome): Pigmentary effector system. VI. The dual character of endocrine coördination in amphibian color change 445
Hohlweg, W.: cf. Schoeller.....684
Horak, J.: Case of Addison's disease successfully treated with cortin and adrenal cortex extract 285
Horsters, H.: The effect of gland preparations on the metabolism of rabbit 202
Horwitz, F.: cf. Bertram.....587
Hoskins, R. G. (Jellinek): Studies on thyroid medication. I. Some conditions determining the haematopoietic effect 455
Houssay, B. A.: Action of the hypophysis on sex glands of fish and reptiles 581
— (Biasotti): Diabetogenic substance of the anterior pituitary 95
—— Hypophysectomy and pancreatic diabetes in toads 211
—— Pancreatic diabetes and the pituitary in the dog.....678
—— Pancreatic diabetes in hypophysectomized dogs. Diabetic conditions in dogs without hypophysis or pancreas.326
—— Phlorizine diabetes in dogs deprived of their hypophysis.317
—— The hypophyseal substance which increases pancreatic diabetes 690
— (Giusti): Function of the hypophysis and of the region of the infundibulum and tuber in the toad 689
— (Giusti and Lazcano-González): Action of ovarian graft in males on the seminal vesicles..206
——— Hypophyseal implantation and stimulation of the sex glands and function in the toad 690
Houssay, B. A. (Giusti and Lazcano-Gonzales): Implantation of pituitary and hyperfeminization of guinea pigs with ovarian graft...211
——— Influence of ovarian grafts on the seminal vesicles...307
— (Lazcano-González): Pituitary and Bidder's organ 211
—— The hypophysis and Bidder's organ 582
— (Marenzi): Cortical adrenal extract and sensitiveness of adrenalectomized rats to intoxication 200
—— Extract of adrenal cortex protects decapsulated rats against toxins 562
— (Mazzocco and Biasotti): Blood iodine in hyposectomized dogs.690
— (Royer and Orias): Hemoglobin and red blood cells of hypophysectomized dogs 212
Hoxie, G. H.: A case of parathyroid deficiency 358
Huddleston, O. L.: cf. Whitehead..312
Humphrey, R. R.: Studies on sex reversal in Amblystoma. V. The structure of ovaries of A. tigrinum subjected for long periods to the influence of a testis resident in the same animal 206
Hunscher, H. A.: cf. Donelson.....304
Hurd, G. B.: cf. Novak.....319
Hurst, A. F. (Cosin): Hyperparathyroidism with hyper calcaemia and decalcification of bones.....101
Hurxthal, L. M. (Menard): Cardiovascular system in goiter.....104
Hutton, J. H.: Relation of endocrine disorders to industrial medicine..567
Hyman, A. S.: cf. Parsonnet.....217

Ihrke, I. A. (D'Amour): The influence of testis hormone upon the oestrous cycle in the rat.....441
Ingham, S. D. (Nielson): Thyroid psychosis. Difficult in diagnosis..453
Ionesco, D. (Bernard and Enachesco): Contraction of the spleen induced by insulin 697
Irwin, O. C.: cf. Nice.....439
Istanamowa, T. (Chudoroschewa): Action of adrenaline on the red blood picture 299

Jacobs, H. R. D.: cf. Samson.....677
Jackson, A. S.: Blood picture in six hundred cases of goiter.....593
Jackson, C. M. (P'an): Effects of dietary deficiency of iodin upon thyroid and parathyroid glands in the rat 146
— (Smith): The effects of deficient water-intake on the growth of the rat 83
Jacobsohn, K.: cf. de Mira.....300

Jaffe, H. L. (Bodansky and Blair): Rate of decalcification and the sites of bone lesions in experimental hyperparathyroidism 590
Janoschek, A.: cf. Staffe.....442
Janssen, S. (Loeser): Pituitary anterior lobe powder and ovary....212
—— The efficiency of the anterior pituitary lobe by oral administration 96
Jaquerod: The treatment of Basedow's disease with myxedematous goiter 452
Jedrzejowska, A.: cf. Arthus..450, 700
Jellinek, E. M.: cf. Hoskins.....455
Jenkins, T. A.: cf. Steinhaus.....569
Johnson, Adelaide: cf. Johnson....299
Johnson, G. E. (Challans): Ovariectomy and corpus luteum studies on rats and ground squirrels.....278
Johnson, J. L.: cf. Wilder.....102
Johnson, V. (Johnson): The secondary rise in blood pressure following peripheral splanchnic nerve stimulation 299
Johnston, R. L.: cf. Lower.....574
Jolly, J. (Lieure): Influence of castration on the involution of the thymus 701
—— Influence of pregnancy on thymus 102
Joltrain: Use of insulin in vagotonia and sensitization to insulin..448
Jonas, L.: cf. Leopold 590
Jones, C. M.: cf. Urmy 449
de Jongh, S. E.: Action of the sex hormone of the hypophysis on male animals 318
— (Laqueur): Antagonism of menformon and hormones of anterior lobe of the pituitary.....318
— cf. Dingemanse 580, 681
— cf. Freud 87, 682
Jordi, A.: cf. Abelin.....702
Jourdan, F.: cf. Tournade 677
Jung, A.: cf. Leriche 591
Juhn, Mary (Barnes): The feather germ as indicator for thyroid preparations 333

Kabak, J. M.: Masculine sex hormone from urine and its assay by the comb method 307
Kahn, R. H.: A note on the problem of the oestrus-cycle in parabiotics 307
Kaiwa, T.: cf. Yen.....201
Kaldor, J.: cf. Goldzieher..... 94
Kallas, H.: Hyperfeminization, the anterior lobe of the hypophysis and parabiosis 690
— (Lipschütz): Hyperfeminization in rabbits 308
— cf. Lipschütz 90
Karlik, L. N. (Robinson): The relation between the pituitary and tuber cinereum. The essential nature of the pituitary 691
Karplus, H.: Silver impregnation of the capillary endothelium of the anterior lobe of the hypophysis...318
Kay, H. D.: cf. Taylor 330
Kehl, R.: Action of mammalian folliculin on the oviduct of turtles...4 1
— cf. Courrier 572
Keller, J.: cf. Hochrein.....437
Kelly, G. L.: Effects of injections of female sex hormone (oestrin) on conception and pregnancy in guinea pig 88
Kemp, W. N.: Treatment of early vomiting of pregnancy with suprarenal cortex. With case reports..434
Kenyon, Josephine H.: Hyperglycemia in hypopituitarism, with glandular treatment 582
Kepinov, L. (Petit-Dutaillis): Physiological studies on insulin..... 99
Kepler, E. J. (Boothby): Creatinuria in hyperthyroidism 104
Kimball, O. P.: Prevention of goiter in Detroit and Cleveland.....594
Kirby, D. B.: Calcium in relation to cataract. I. In vitro.....328
— Calcium in relation to cataract. II. In vitro 328
Kiss, A.: The locally limited action of hormones, particularly that of pituitrin, upon the water exchange 212
Klein, M.: Effects of injections of an active material extracted from the corpus luteum on the genital tract of normal and castrated females 573
— Reactions of the ovary to the injections of the placenta. Is the substance in the placenta which reacts on the ovary a hormone of the anterior lobe of the hypophysis? 683
Klein, O.: cf. Asher 199
Klein, W.: Specific dynamic action in Graves' disease 706
Knude, M. M. (D'Amour, Gustavson and Carlson): The effect of estrin administration on the reproductive and blood vascular systems: the thyroid, thymus, hypophysis, adrenals, kidneys, liver and spleen 203
Kober, S.: cf. Dingemanse.....205, 572
Koch, F. C.: Extraction, distribution and action of testicular hormones 441
— cf. Womack 267, 273
Koehler, A.: cf. Zerfas..... 82
Komant, W.: The diazo-reaction of thyroxine and its inhibition by constituents of the blood.....222
Kommerell, B.: The dependence of thyroxine effect upon nutrition...594
Korabelnikowa, A.: cf. Stschedrowitzky 569
Koskoff, Y. D.: cf. Himwich....99, 216
Koskowski, W.: cf. Gedroyc.....297

Koster, H. (Goldzieher, Collins and Victor): Operative treatment of adrenal cortical obesity 562
Kostowiecki, M.: The relations between Hassalls corpuscles and the blood vessels in the thymus of the human foetus 331
Kotowa, O.: cf. Larionov 567
Kraft, Ruth: cf. Nice 439
Krantz, J. C.: cf. Silver 449
Kraul, L.: Certain new observations on the action of the anterior pituitary 691
Kraut, H.: cf. Frey..... 98
Krizenecky, J.: New experiments on the antagonism between the thymus and the thyroid 594
Kun, H.: cf. Novak.....694
Kunde, M. M. (Greene and Burns): Blood changes in experimental hypo- and hyper-thyroidism (rabbit).707
Kurzrok, R.: Estimation of estrin and the follicle-stimulating hormone in urine as an index of therapy in menstrual dysfunction 361
— Follicular hormone in urine as index of therapy in menopause.366
Kuschinsky, G.: Studies on sympathol, a new adrenalin-like substance 438

La Barre, J.: Variations in insulin secretion during intrapancreatic hyperglycemia. Variations in insulin secretion during extrapancreatic hyperglycemia 697
— (des Cespédes): Variations in gastric secretion during insulin hypoglycemia 697
— (Boolemen): The influence of intense secretory activity in the pancreas on reduction of blood sugar by insulin. On the causes of the reduction in output of insulin secretion seen during excessive external secretion of the pancreas.....588
— cf. Zunz 570
La Barre, Jean (Patalano): Note on the coagulation properties of the posterior lobe of the hypophysis..445
Labbe, M.: Diabetic resistance to insulin treatment 216
— (Escalier and Dreyfus): Acromegaly and diabetes 318
Laclau, N. C.: Growth of tumors in decapsulated white rats 676
Lacqueur, E.: cf. de Jongh.....318
Laffont, A.: Indications and technique for the sterilization of the woman-procedure. Biological methods 90
Lambie, C. G. (Wiesner): On the relation between the hormones of the anterior lobe of the pituitary and clinical syndromes 318
Laqueur, E.: cf. Dingemanse.....
.....205, 572, 681
— cf. Freud 87, 682
Larionov, W. T. (Kotowa): Condition of the thyroids of pigeons fed desiccated anterior hypophysis...567
Lascano-Gonzales, J. M.: cf. Houssay 307, 582, 690
Lauber, H. J. (Ramm): Prognosis and therapy of arthropathia ovaripriva 308
Laurent, Y.: cf. Rathery 326
Lautier, R.: Contribution to the study of the etiology of goiter...333
Lawrence, R. D. (McCance): The effect of starvation, phloridzin, thyroid, adrenalin, insulin and pituitrin on the distribution of glycogen in the rat.....567
Lazarus, J. A. (Eisenberg): Tumors of the adrenal gland 563
Lazcano-González, J. M.: cf. Houssay 211
Lazcano-González, L.: cf. Houssay.206
Lechelle, P.: cf. Guillain.....316
Le Grand, A. (Ramos): The action of synthetic thyroxin on the chronaxie of "gastrocnemiusscciatic" preparations of Rana temporaria 333
Leites, S.: Thyroxin, fat and lipoid metabolism 333
Lemaire, A.: cf. Loeper.....334, 676
Leonard, S. L.: The nature of the substance causing ovulation in the rabbit 308
— cf. Meyer 655
Leopold, E. J.: Diabetes in the negro race 216
Leopold, S. S. (Jonas): Chronic adult idiopathic tetany 590
Lepine, P.: Effect of extracts of the anterior lobe of the hypophysis when given by mouth 691
— Effect of large doses of anterior hypophysis lobe extract on the reproductive ability of the rat..582
— The comparative action of extracts of the anterior lobe of the hypophysis on the appearance of puberty and growth in rats and mice 691
Leriche, R. (Jung): Treatment of scleroderma by parathyroidectomy 591
Lerman, J. (Brogan): Renal function in exophthalmic goiter and myxoedema 251
— (Means): Gastric secretion in exophthalmic goiter and myxoedema 707
— — Iodin in exophthalmic goiter. A comparison of the effect of ethyl iodid and potassium iodid 104
— — Treatment of anemia of myxoedema 533
— cf. Means 105
Leschke, E.: Importance of sympathetic system in metabolism.....678

Lesne, E. (Dubois and Simonnet): The effect of irradiated ergosterol on tentany resulting from parathyroidectomy in rabbits.....700
Levin, L.: cf. Thayer.....576
Levine, S. E. (Marples): The respiratory metabolism in infancy and in childhood. XII. A biometric study of basal metabolism in normal infants 568
Leulier, A. (Revol): The distribution of lipoidal phosphorous in the adrenal glands of certain mammals 676
Levai, M.: Oral administration of bismuth-insulin for gastroduodenal troubles 697
Lewis, J. K. (McEachern): Persistence of an accelerated rate in the isolated hearts and isolated auricles of thyrotoxic rabbits; response to iodides, thyroxine and epinephrine 105
Lichtenstern, R.: The lasting effects of transplanted testicles.....683
Lieure, C. (Bonciu): Studies on the histogenesis of the thymus. Histologic reconstruction of thymus grafts 701
— cf. Jolly 102, 701
Lipschütz, A.: Experimental basis of ovarian transplantation 207
— Note on the biological estimation of folliculin 684
— On some fundamental laws of the dynamics of sex 90
— Terminology of the female sexual hormone 573
— The follicular hormone 90
— (Kallas): New experiments on the transplantation of dried ovary 90
— (Veshnjakov): On the occurrence of oestrin in the urine of the pregnant cow 573
— — Oxygen use of the isolated ovary of the mammal 90
— (Veshnjakov and Wilckens): Folliculin in the urine of pregnant cows 684
— cf. Kallas 308
Lison, L.: cf. Gerard 298
Lisser, H.: cf. Reilly 337
Lockwood, J. E.: cf. Hartman.....521
Lockwood, W. W.: cf. du Vigneaud.699
Loeb, L.: Specificity in action of anterior pituitary of different mammals as well as of urine of pregnant women on sex organs and thyroid glands of immature female guinea pigs 129
Loeb, R. O. (Shorr and Richardson): Responses to injection of epinephrine in hepatic disease 203
Loeper, M. (Lemaire and Patel): Effect of adrenin and acetyl-choline on the pressure of the spinal fluid 676
Loeper, M. (Lemaire and Tonnet): Effect of certain therapeutic measures on the protein equilibrium of the thyroid 334
Loeser, A.: Pharmacological method for the valuation of the action of the anterior lobe of the hypophysis 318
— Properties and durability of powdered anterior pituitary lobe..582
— cf. Janssen 96, 212
Loewe, S. (Ross and Rothschild): The coexistence of the male and female sex hormone 684
Lomas, C. H.: cf. Turner..... 92
Long, J. A.: cf. Pencharz.....575
Long, M. Louisa: cf. Bischoff..297, 313
Lopatina, E.: cf. Stschedrowitzky..569
Louyot, P.: cf. Santenoise.....698
Lower, W. E. (Johnston): Further studies on experimental work on probable causes of prostatic hypertrophy 574
Luchs, A.: cf. Dingemanse.....205
Lucien, M. (Bleicher): Determination of the area for irradiation of the adrenal gland 299
Lukacs, J.: Does the hormone of the thyroid gland pass into the mother's milk? 222
— Effect of insulin and epinephrine on the sugar content of the cerebrospinal fluid 448
Lundstrom, Helen M. (Bard): Hypophysial control of cutaneous pigmentation in an elasmobranch fish 691
Lutz, B. R.: cf. Wyman.....677
Lyons, W. R. (Van de Carr): Immunologic aspects of the sexual cycle; anaphylactic studies with mammalian follicular fluid.....574

MacCarty, W. C.: Pathological classification of goiter and its clinical significance 453
MacDowell, E. C.: cf. Smith.....213
Macht, D. I. (Stickels): Effect of oestrin and lutein combinations on uterus of the mouse 441
Macy, I. G.: cf. Donelson.....304
Mahler, P. (Beutel): Effect of parathyroid extract on tonus and peristalsis in the stomach and intestines 329
Maiman, R. M.: The centers of the hypophysis cerebri 692
Maino, M.: Absorption of follicular hormone through the mucous membrane of the gastro-intestinal tract 309
— cf. Frattini 87
Maino, M. M.: Gastric absorption of the follicular hormone 207
— cf. Frattini 307
Malmejac, J.: Tournade.....302, 565
Mandl, G.: Acute suprarenal insufficiency with aspects of acute peritonitis 79

Mann, F. C.: cf. Bollman.....696
— cf. Priestley 223
Manoukine, J.: The spleen, an endocrine organ 701
Marañon, G.: The critical intersexualities 89
Marenzi, A. D.: cf. Houssay...200, 562
Markowitz, B.: Focal cyclic growth as a factor in production of nodular goiter 594
— Pathogenesis of goiter.....594
Markowitz, J.: cf. Priestley.....223
Marks, H. P.: cf. Corkhill 199
Marples, E.: cf. Levine.....568
Martin, E.: The inhibitory action of "Prolan" (pituitary anterior lobe hormone) 212
Martin, S. J.: cf. Meyer.....655
Martins, R. (Cardoso): Seminal vesicle grafts in mice.....574
Martins, T.: Functional differences in the hypophysis associated with sex 319
— Influence of the seminal epithelium on the hypophysis 309
— Ovulation and precocious puberty following parabiosis 582
— Parabiosis and ovarian grafts...684
— The use of rabbits to test the hypophyseal hormone and that of pregnancy 693
— (Fabiao): Ovulation in pregnant rabbits after the injection of urine from pregnant women...309
— (Rocha): Effect of castration, grafts and implantation of the gonad on the anterior lobe of the hypophysis 445
— (Rocha): Regulation of the hypophysis by the testis 583
— — Regulation of the hypophysis by the testicle. Experiments with parabiosis 693
Matsubara, M.: The secretion of the small intestine. II. The effect of insulin and adrenaline upon the secretion of the small intestine and its mechanism 302
Mauriac, P.: Action of insulin on the increased blood cholesterin in nephritic rabbits 588
Mavromati, L.: cf. Daniel.....681
— cf. Parhon 106
Mayer, L. H.: Treatment of diabetes mellitus in the presence of other acute febrile diseases..... 99
Mazzocco, P. (Arias-Aranda): Iodine content of the air, soil, water and food in a region of endemic goiter. The quantity of iodine eaten daily by the inhabitants of Salta. Iodine content in sheep thyroids in the province of Salta and along the sea-coast 707
— cf. Houssay 690
McCance, R. A.: cf. Lawrence.....567
McClendon, J. F. (Myrick, Conklin and Wilson): Ovarian hormone and metabolism 89
McEachern, D.: cf. Lewis.....105
McGowan, J. P.: On the nature and structure of the suprarenal cortex.563
McGovern, B. E.: Epileptoid attacks and hyperinsulinism 293
— Somnolence associated with pituitary cachexia 402
McHenry, E. W.: cf. Ettinger..... 93
McIntyre, A. R. (Van Dyke): The distribution and concentrations of water and halides in the blood and urine during diuresis-inhibition by pituitary extract 319
McJunkin, F. A. (Rall and Singer): Effect of adrenaline chloride on the proliferative activity of the cells of the adrenal medulla.....635
McKinney, J.: The Lawrence-Biedl syndrome 693
McLean, S. (Caffey): Endemic purpuric meningococcus bacteremia in early life. The diagnostic value of smears from the purpuric lesions 438
McPhail, M. K.: cf. Collip..... 86
McQuarrie, I. (Peeler): The effects of sustained pituitary anti-diuresis on epilepsy 693
Means, J. H. (Lerman and Castle): Co-existence of myxedema and pernicious anemia 105
— cf. Lerman 707, 533, 104
Menard, O. J.: cf. Hurxthal 104
Merland, P. A.: Golgi apparatus and vacuoles in the adrenal of pregnant guinea pigs 676
Metz, R. D.: Insulin in malnutrition.448
Meyer, H. H.: Place and manner of thyroxin action 708
Meyer, P. E.: The action of insulin on gastric secretion 217
Meyer, R. K. (Leonard, Hisaw and Martin): Influence of oestrin on gonad-stimulating complex of anterior pituitary of castrated male and female rat 655
Meyer, K.: cf. Evans 444
— cf. Reichert 445
Meyer-Nobel, K.: Influenciation of a case of diabetes insipidus through corpus luteum extract...326
Migliavacca, A.: Effect of insulin on the ovary 309
Milcou, S. M.: Should the carotid body be classed as a paraganglion? 300
Milhaileanu, C.: cf. Gavrila.....689
Mills, C. A.: Climate as a potential factor in the etiology of exophthalmic goiter and other metabolic diseases 52
— Diabetes mellitus; sugar consumption in its etiology 99
de Mira, F. (Fontes and Jacobsohn): Effect of an extract from the adrenal cortex on the survival of decapsulated guinea pigs 300
— — Effect of extracts of the adrenal cortex on the survival of decapsulated guinea pigs....438

Miyake, T.: The influence of the thyroid gland upon the poisonous action of various drugs.....334
Mohler, H. K. (Goldburgh): Diabetes mellitus with resistance to insulin and failure to obtain clinical improvement from its use. Report of cases 697
Molfino, F.: Glycemia in relation to x-ray irradiation of the adrenal 676
Moller, K. O.: Dietetic treatment of hyperthyreosis 334
Monguio, J.: cf. Weiss.....591
Montpellier, J. (Chiapponi): Effect of folliculin on the anterior lobe of the hypophysis 568
Moore, C. R. (Price): Some effects of fresh pituitary homo-implants and of the gonad-stimulating substance from human pregnancy urine on the reproductive tract of the male 583
— — Gonad hormone functions, and the reciprocal influence between gonads and hypophysis with its bearing on the problem of sex-hormone antagonism 574
— (Samuels): The action of testis hormone in correcting changes induced in the rat prostate and seminal vesicles by vitamin B deficiency or partial inanition..441
Moore, R. M.: cf. Cannon.....439
Mora, J. M.: Periodic paralysis occurring in course of exophthalmic goiter 407
Morato, M. J. X.: Some results with the use of the silver impregnation method in studying the hypophysis 212
Moritz, A. R. (Bayless): Papilliferous tumors of the thyroid gland and of aberrant thyroid tissue....708
Morris, R. S.: Thyrotoxic circulatory symptoms with low metabolic rate 595
Morse, Dorothy L.: cf. Fluhmann..306
Morse, Jean R.: cf. Dorn.....572
Mouriquand, G. (Bernheim): The physiologic and pathologic rôle of the thymolymphatic system.....701
Mowrer, O. H. (Casey): A note on relationship between nystagmus duration and thyroid condition....431
Moxon, G. F.: cf. Murphy..... 99
Moya, A.: cf. Bonilla.....704
Mukherjec, H. N.: The production of hypoglycemia in rabbits by oral administration of precipitated insulin 217
Müller, C.: Experimental justification for the functional relation of the adrenal cortex to the sex organs 300
Münch, A. P. W.: cf. Dingemanse.. .....205, 572
— cf. Freud 87
Munteanu, N.: cf. Nitzescu.....583
Murphy F. D. (Moxon): Diabetes mellitus and its complications. An analysis of 827 cases 99
Myrick, L.: cf. McClendon..... 89

Nahum, L. H.: cf. Himwich...99, 216
Nastase, A.: cf. Zaharescu-Karaman 443
Nelson, W. O. (Pfiffner): Studies on physiology of lactation. I. Relation of lactation to ovarian and hypophyseal hormone 84
— cf. Haterius 689
Neumann, H. O.: Anterior hypophyseal hormone (prolan) and the male gonad 319
Neumark, S.: Effect of insulin on the blood cholesterine in non-diabetics 303
Nevalonnyj, M. (Podhradsky): Influence of thyroid and thymus on skeleton formation in Italian partridges 105
Nibler, C. W.: cf. Turner..... 92
Nice, L. B. (Irwin and Kraft): Coagulation time of the blood of adrenalectomized 439
— cf. Friedman 307
Nielson, J. M.: cf. Ingham.....453
Nitzescu, I. I.: Effect of different substances from the posterior lobe of the hypophysis on the coagulation of the blood 319
— Effect of parathyroid extract injected into the cerebro-spinal fluid 700
— (Benetato): The action of hypertensive and ocytocic substances from the posterior lobe of the hypophysis on the fat in the blood 212
— (Munteanu): The mechanism of the action of pituitrine. Effect of extracts and of substances of the posterior lobe of the hypophysis on the lactic acid of the blood 583
— (Popoviciu): On the action of irradiated ergosterol and its products on tetania parathyreopriva 591
Noether, P.: Pituitary and ovulation in the hen.....583
Nonidez, J. F.: The origin of the "parafollicular" cell, a second epithelial component of the thyroid gland of the dog.....708
Novak, E. (Hurd): The use of an anterior pituitary luteinizing substance in the treatment of functional uterine bleeding.....319

Novak, J. (Kun): Researches with anterior lobe of the hypophysis from urine of pregnancy and with anterior lobe pituitary substance upon various experimental animals 694
Novick, N.: Native complement in hyperthyroidism 105

Ochsner, A.: cf. Gage.....588
Ohato, S.: On the adrenalin content in suprarenals and the amount of the adrenalin-like substance in the serum of guinea-pigs fed on vitamin C free diets.....439
Ohguri, M.: On effect of uni and bilateral suprarenalectomy upon some blood constituents of rabbits 200
— The effect of the removal of the suprarenals and accessory cortical tissues together upon some blood constituents of rabbits..203
Oikawa, K.: The susceptibility of doubly suprarenalectomized rabbits to nicotine, histamine, ephedrine and typhoid vaccine 439
Okkels, H.: The Golgi apparatus in the thyroid cells in Basedow's goiter 709
O'Leary, W. D.: Carbohydrate metabolism in Mongolian idiots as evidence of endocrine dysfunction 84
— Carbohydrate metabolism in Mongolian idiots as evidence of endocrine dysfunction 204
Oliveira, C.: cf. Coelho.....451
Olivet, J.: The diuretic hormone of the brain 320
Orias, O.: cf. Houssay.....212
Ornsteen, A. M.: A contribution to the pathogenesis and heredity of the Laurence-Biedl syndrome....583

Paal, H.: Thyroid function and the Reid Hunt reaction 453
Page, I. H.: (Pastermak): Influence of adrenaline on the blood and organ lipoids 200
Paik, T. S.: On relation between parathyroid hormone and growth of rat carcinoma 701
Pall: Histophysiology of hormone products 85
Palmer, H. D. (Harrow and Schwartz): Osteitis fibrosa cystica of the skull associated with heminaopia psychotic symptoms..701
P'an, M. T.: cf. Jackson.....146
Parfentieff, I. (Sokoloff): Studies on the lipolytic power of the adrenal gland 439
Parhon, C. I. (Ballif and Stirbu): Action of serum from a male animal on combs of capons..... 91
— — Studies of the effects of serum from acromegalics on the growth of young animals....212
Parhon, C. I. (Cahane): Calcium content of the brain and kidney of animals receiving Collip's parathormone 219
— — The calcium and water content of cardiac muscle in hyperthyroidized animals 453
— (Derevici): The syndrome developing after simultaneous removal of the thyroids, parathyroids and testes. Survival time and changes in blood chemistry.223
— (Derevici and Derevici): Effect of bleeding and of a single injection of Collip's parathormone on blood. Calcium, sugar and cholesterin in normal hyperthyroid and thyroidectomized animals 595
— (Marie Briese): The presence of a virilizing substance in the urine of a young woman suffering from virilism 309
— (Mavromati): The resorption of physiologic solution injected intradermally and subcutaneously in a myxodematous idiot. Relation between the thyroid and tissue fluid 106
— (Werner): Brain phosphorous in experimental hyperthyroidism..223
— — Phosphorous content in the brain and spinal cord of animals after repeated injections of adrenin 677
— — On the total phosphorus of the brain and spinal cord of dogs treated with thyroid gland, tryroxin, parathyroid hormone or with thyroid and parathyroid combined 595
— — Studies on the condition of phosphorous in parathyroidectomized and thyroparathyroidectomized animals 101
— cf. Teitel-Bernard 589, 699
Parhon-Stefanesco, C.: Increase in transparency of bones when x-rayed, after injections of Collip's parathormone 701
Parkes, A. S.: cf. Hill.....210, 690
Paroli: Research studies and clinical results on diathermy of the thyroid on the essential metrorrhagias 595
Parsonnet, A. E. (Hyman): Insulin angina 217
Parvey, B.: Recent advances in physiology of reproduction in relation to Zondek-Aschheim test for the early detection of pregnancy.225
Pasternak, L.: cf. Page.....200
Patalano, A.: cf. La Barre.....445
Patel, J.: cf. Loeper.....676
Peck, R. I.: cf. Barlow.....447
Peckham, C. H.: Diabetes mellitus and pregnancy 698
Peeler, D. B.: cf. McQuarrie.....693
Pekarek, E.: cf. du Vigneaud.....699

Pellegrine, G.: The action of ether extracts of testicular powder on castrated fowls 575
Pemberton, J. deJ. (Willius): Cardiac features of goiter 709
Pencharz, R. I. (Long): The effect of x-raying one ovary of a rat on a subsequent pregnancy after removal of the normal ovary during the course of gestation 575
— cf. Reichert 445
Penna de Azevedo, A.: cf. Villela..711
Perez, M. L.: Studies on the cause of parturition in women.....310
Perla, D. (Gottesman): A substance in urine of normal human adults that raises the resistance of suprarenalectomized rats 80
— — Effect of injections of cortin on resistance of suprarenalectomized rats to histamine poisoning 80
— — Injections of cortin on resistance of suprarenalectomized rats. Biological assay of extracts of suprarenal cortex.. 79
— cf. Gottesman 78
Petit-Dutaillis, S.: cf. Kepinov..... 99
Petzetakis, M.: Effect of intravenous injections of adrenin on heart. Terminal fibrillation. Electrocardiographic studies 563
Pfiffner, J. J.: cf. Greene.....675
— cf. Nelson 84
— cf. Rowntree 300
— cf. Swingle 81, 564
Philipp, E.: Anterior pituitary and placenta 584
— The site of formation of the "anterior pituitary" hormone in pregnancy 96
Phillips, R. A.: cf. Freeman.....202
Pietsch, K.: Structure and development of pars tuberalis of the human hypophysis and its relation to the other portions of the hypophysis 320
Pike, F. H.: cf. Coombs.....560
Plaut, A.: The hypophysis of an orang-utang, together with remarks on the so-called pars intermedia of man and man-like apes.321
Plummer, H. S.: Incidence of exophthalmic goiter in Olmstead County, Minn. 106
Podhradsky, J.: Influence of thyroid and thymus on growth of castrated and non-castrated Italian partridge cocks 107
— cf. Nevalonnyj 105
Poleff, L.: Action of adrenin on local immunization with staphylcoccus antivirus 677
Polhemus, Irene: cf. Riddle 446
Popoff, H.: Collection of illustrative cases of hypophyseal infantilism 445
Popoff, N. W.: Testicular tubular adenoma of the ovary; its eiologic relation to embryonic vestiges and spontaneous sex reversal of the female gonads. Report of a case..310
Popoviciu, G.: cf. Nitzescu.....591
Potick, D. (Re): Triptophane in blood and tissues after thyroidectomy and pancreatectomy.....204
Potter, I. W.: cf. Hartman.....155
Pratt, J. P.: Ovarian therapy..... 45
Price, Dorothy: cf. Moore.....574, 583
Priestley, J. T. (Markowitz and Mann): The tachycardia of experimental hyperthyroidism 223
Ptasker, L.: Effect of diathermy on the basal metabolism as an indication of the hormonal activity of the testes in dogs. Use of the diathermic reaction for the study of testicular insufficiency following resection of the ductus deferens 442
Ptaszek, L.: cf. Elmer.....580
Pucsko, O.: The influence of injections of sucrose and invert sugar upon ketonuria and ketonemia in diabetes mellitus 326

Racchiusa, S. (Crisera): The so-called influence of the suprarenal medulla on alimentary hyperglycemia 201
Räihä, C. E.: Effect of insulin on the thyroid gland 453
— (Grönlund): Action of insulin on intra-ocular pressure 698
Raik, T. S.: Relationship between the parathyroid hormone and the growth of rat carcinoma.....219
Rall, R.: cf. McJunkin.....635
Ramm, C.: cf. Lauber.....308
Ramos, S.: cf. LeGrand 333
Raspopova, N.: On the action of thyroid gland and of thyroxine on moulting and feather structure in geese 595
Rathery, F. (Gibert and Laurent): The delayed variations in the glycogen of the liver.....326
— — The late variations in liver and muscle glycogen in depancreatized dogs given repeated doses of insulin.....326
Ratti, P.: cf. Asher.....220
Raynaud, R.: The sensibility of auto grafts of vaginal mucosa of guinea pigs to folliculin 207
Re, P. M.: cf. Potick.....204
Regnier, V.: cf. Caridroit.....304
Reichert, F. L. (Pencharz, Simpson, Meyer and Evans): Ineffectiveness of Prolan in hypophysectomized animals 445

Reicker, H. H.: A clinical study of myxedema in Michigan.....595
Reilly, W. A. (Lisser): Laurence-Moon-Biedl syndrome.....337
Reinwein, H.: Observations on the complex symptoms which accompany hypoglycemia.....326
Reiss, M.: Studies on the function of the adrenal cortex. III. Adrenal cortex and cholesterol metabolism 300
Reiss, M. (Haurowitz): Chemistry of the sex horomone of the anterior lobe of the pituitary gland.... 96
— (Selye and Balint): Concerning the luteinizing principle of the anterior lobe of the hypophysis. 96
— — The effect of anterior pituitary luteinizing hormone on the male genital organs.....321
Reveno, W. S.: The cause of exophthalmic goiter; a biochemical hypothesis 454
Revol, L.: cf. Leulier.....676
Reynolds, S. R. M.: Humoral factors affecting uterine motility.....193
— Studies on the uterus. V. The influence of the ovary on the motility of the non-gravid uterus of the unanesthetized rabbit....442
Ribiere, M. (Chiapponi): A convenient method for extracting folliculin 310
Richardson H. B.: cf. Loeb.....203
Riddle O. (Braucher): Studies on the physiology of reproduction in birds. XXX. Control of the special secretion of the crop-gland in pigeons by an anterior pituitary hormone 321
— (Polhemus): Studies on the physiology of reproduction in birds. XXXI. Effects of anterior pituitary hormones on gonads and other organ weights in the pigeon 446
Riser M. (Sorel): Studies on the cerebral circulation. Action of adrenin 201
Riskin, A. M.: cf. Barnes.....450
Ritter, J.: The duality of diabetes mellitus and pulmonary tuberculosis 588
Robinson, I. A.: cf. Karlik.....691
Rocha, A.: cf. Martins.....445, 583, 693
Rocheta, J.: cf. Coelho 221
Roeder, P.: cf. Bland.....679
Rogemont, L.: Variations in the sugar level in castrates.....207
Roholm, K.: Clinical investigations into the effect of intravenous injection of insulin. V. The action of adrenalin upon the stomach secretion 300
Rony, H. R.: Juvenile obesity.....601
Rosenberg, M.: Snuff-powder therapy of diabetes insipidus with various posterior pituitary preparations...322
Rosenblueth, A.: The sensitization by cocaine of gastric and uterine smooth muscle to the inhibititory action of adrenin 201
— (Cannon): Studies on conditions of activity in endocrine organs. XXVIII. Some effects of sympathin on the nictitating membrane 679
Rosenfeld, S. (Durrant): Effect of ovarian substances on excised rat uterus 684
Rothschild, Eva: cf. Loewe.....684
de Rudder, B.: Simmond's hypophyseal cachexia in childhood.....694
Roux, J.: cf. Barral.....587
Rowe, A. W.: Possible constitutional elements in the behavior problems of the young.....303
— Vital function studies. VIII. Weight calculation in pregnancy 91
Rowntree, L. G. (Greene, Ball, Swingle and Pfiffner): Treatment of Addison's disease with cortical hormone of suprarenal gland.....300
— cf. Ball.....559
— cf. Greene.....675
Royer, M.: cf. Houssay.....212
Rucker, M. P.: The action of thymophysin on the human pregnant uterus in situ.....102
Ruckert, W.: cf. Burger..... 98
Ruedemann, A. D.: Ductless glands as they appertain to eye diseases and to surgery.....568
Ruiz, R.: New form of Hodgkin-Paltauf-Sternberg's disease; Addison's syndrome and granulomatosis 563
Rywkin, I.: cf. Berliand.....332

Sacharoff, V.: On the action of the thyroxine on the bile secretion...596
Sainton, P. (Simonnet): Familial over thyroidizing in chickens.....596
Sakamoto, A.: Myasthenia gravis and internal secretion.....204
Sakharoff, G. P.: Shall the spleen be considered as an organ of internal secretion? 591
Samson, P. C. (Jacobs): Some chemical effects from constant intravenous epinephrine injections in dogs 677
Samuels, L. T.: cf. Moore.....441
Sanes, S.: cf. Terplan..... 69
Santenoise, D. (Brieu, Fuchs, Louyot and Vidacovitch): Association of vagotonic pancreatic extract (vagotonic hormone) with insulin in diabetes 698
— (Verdier and Vidacovitch): Insulin and liver glycogen.....696
— cf. Brieu.....696
Sapegno, E.: cf. Ceruti.....216
Sarafanov: cf. Zavadovsky.....324
Savitsky, N.: cf. Wechsler.....335
Scaglione: Fibroma of the uterus and hypophysis 584

Schäfer, W.: The effect of anterior pituitary lobe upon growth and fat accumulation 694
Schapiro, B.: Clinical observations on the action of the sex stimulating hormone of the anterior lobe of the pituitary upon male genitalis 694
Schiempflug, W.: cf. Staffe 442
Scherer, L. R.: cf. Allan.....417
Schereschewsky, M.: The suprarenal-genital syndrome of Cooke-Apert-Gallais 564
Scheringer, W.: cf. Bokelmann.....450
Schilephake, E.: Relation of the thyroid to the spleen.....454
Schmidt, L. H.: cf. Tashiro.....710
Schnabel, T. G.: Hyperparathyroidism with osteitis fibrosa cystica (parathyroid hyperplasia) 101
Schockaert, J.: Note on the stimulating action of extracts of the anterior lobe of the hypophysis on the thyroid. Specific action of extracts of the anterior lobe of beef hypophysis on the weight of the thymus in young ducks.....584
Schockaert, J. A.: Enlargement and hyperplasia of the thyroids in the young duck from the injection of anterior pituitary.....569
Schoeller, W. (Dohrn and Hohlweg): The peroral effect of the follicular hormone 684
Schteingart, M.: cf. Castrex.....315
Schultz, F.: cf. Frey..... 98
Schultze, A. B.: cf. Turner.....443
Schwartz, L. A.: cf. Palmer.....701
Schwarz, O. H. (Drabkin): Basal metabolism rates in late pregnancy and the puerperium 310
Seifert, A. C.: Therapeutic irradiation of the ovaries.....575
Selye, H.: Stimulation of new bone-formation with parathyroid extract and irradiated ergosterol.....547
— cf. Reiss.....96, 321
Serejski, M. J.: Biedl's disease..... 97
Serio, F.: Aspects of diabetes with insulin resistance.....699
Severance, A. O.: cf. White.....311
Sevringhaus, E. L.: A study of five hundred diabetics 100
Shelesnyak, M. C.: The production in young rats following gonadal stimulation with pituitary implants 207
Shelton, E. Kost: Optimal weight estimation 492
Shepardson, H. C.: Glycopenia. The efficiency of high fat diets in treatment of chronic hypoglycemia....182
Sherman, H. C. (Smith): The vitamins 296
Shinsuke, O.: Studies in experimental scurvy. X. On the adrenalin content in suprarenals and the amount of the adrenalin-like substance in the serum of guinea pigs fed on a vitamin C free diet..301
Schockaert, J. A.: Response of male genital system of immature domestic duck to injections of anterior pituitary substances 97
Shookhoff, C.: The coincidental occurrence of diabetes mellitus and pernicious anemia.....699
Shorr, E.: cf. Loeb.....203
Siedentopf, H.: Investigations on the action of thyroxin in pregnancy 107
Siegel, A. E. (Thomas): Primary hypertension in childhood. The influence of hyperadrenalism.....301
Siegert, F.: What effect have the hormones of pregnancy on the growth of the fetus and the changes of pregnancy of the mother? 207
Silver, A. A. (Krantz): The effect of the ingestion of burdock root on normal and diabetic individuals. A preliminary report.....449
Silvette, H.: cf. Britton.....77, 560
Simonds, J. P. (Helpler): Fat tolerance in experimental hyperthyroidism 596
Simonnet, H.: cf. Brouha.....686
— cf. Lesne.....700
— cf. Sainton.....596
Simpson, Miriam E.: cf. Evans.315, 444
— cf. Reichert.....445
Singer, P. L.: cf. McJunkin.....635
Slome, D.: cf. Hogben.....445
Slosse, J.: cf. Demoor.....592
Smith, G. L. M.: cf. Ettinger..... 93
Smith, G. van S. (Smith): Rôle of progestin in female reproductive cycle 576
— — Studies on the urinary excretion of oestrin, with especial reference to the effect of the luteinizing hormone and progestin 310
Smith, J. F.: cf. Gardiner-Hill..... 88
Smith O. W.: cf. Smith.....310, 576
Smith P. E.: Hypophysectomy and replacement therapy in the rat...322
— (MacDowell): An hereditary anterior-pituitary deficiency in the mouse 213
— (White): Effect of hypophysectomy on ovulation and corpus luteum formation in rabbit....576
— cf. Hess.....567
Smith, R. G.: cf. Edmunds 78
Smith S. L.: cf. Sherman.....296
Smith V. D. E.: cf. Jackson..... 83
Snapper, I.: Osseous diseases and the parathyroids.....330
Sokoloff, B.: cf. Parfentieff.....439
Solari, L. A.: Body temperature changes in.....585
— Temperature and thermal reactions of hypophysectomized dogs..213
Sorel, R.: cf. Riser.....201
Soskin, S. (Binswanger and Strouse): Jerusalem artichokes and liver in treatment of diabetes mellitus...326

Soule, S. D. (Brown): Anterior pituitary hormone in the cerebrospinal fluid during pregnancy.....695
Spencer, J. (D'Amour and Gustavson): Effects of continued estrin injections on young rats.....684
—— Further studies on estrin-hypophyseal antagonism in the white rat.....647
Speranska-Stepanova, E. N.: The influence of the thyroid-parathyroid system and the sympathetic nervous system on the blood-serum calcium 709
Spichtin, W.: cf. Abelin.....220
Spiers, M. A.: cf. Himwich.....302
Squier, R. R.: cf. Hartman..... 95
Ssacharoff, P.: cf. Berliand.....332
Staffe, A. (Janoschek and Scheimpflug): The composition and properties of milk from castrated cows 442
Stahl, J.: cf. Aron.....577, 695
Stahnke, E.: Experimental research on the action of thymus extirpation upon goiter production.....331
Stamm, E.: The insulin-sensitivity of nondiabetic humans and its relationship to the vegetative nervous system 217
Stanley, L. L. (Tescher): Weight of gold fish influenced by testicular substance diet.....153
Starns, C. E.: The symptomatology of hypothyroidism 223
Steel, J.: The properties of the adrenal lipoid.....677
Stefko, W.: Pathology of the thymus and thyroid gland during inanition 85
Steinhaus, A. H. (Jenkins): Studies in the physiology of exercise. IV. Further concerning exercise and basal metabolism in dogs.....569
Stickels, A. E.: cf. Macht.....441
Sterting, W.: The Lawrence-Biedl syndrome 695
Stevens, J. J.: Roentgen rays and radium in toxic goiter and hyperthyroidism 709
Stirbu, A.: cf. Parhon.....91, 212
Stockinger, W. (Berchtold): Effect of anterior pituitary on leucocyte counts 585
Strauss, I. (Globus): Simmond's disease. Fatal issue; neocropsy findings. Case 6.....323
Streck, A.: The application of oestrous hormone therapy in practice 311
Strecker, E. A.: Hypopituitary disease with hemiplegia, hypertension, and an atypical sugar tolerance curve.....585
Stricker, P. (Grueter): Anterior lobe of the hypophysis and rupture of the follicle in rabbits.....213
Strouse, S.: cf. Soskin.....328
Stschedrowitzky, S. G. (Lopatina and Korabelnikowa): The part played by the endocrine glands in active immunity 569
Sturn, A.: Respiration of the thyroid gland 107
Suden, Caroline, T.: cf. Wyman... 81
Sugarman, E. I.: cf. Dorn.....572
Sugiura, K.: Further study on the influence of an aqueous extract of suprarenal cortex on the growth of carcinoma, sarcoma and melanoma in animals 201
Swezy, Olive: cf. Evans 305
Swingle, W. W. (Pfiffner): On the cortical hormone of the adrenal gland 81
—— Studies on the adrenal cortex; further observations on preparation and chemical properties of cortical hormone...564
— cf. Greene 675
— cf. Rowntree 300
Szarka, A.: The influence of the oestrus cycle on the basal metabolism of rat 208

Tada, H.: On the hypoglycaemic action of insulin upon doubly suprarenalectomized rabbits 588
Tashiro, S. (Schmidt): The relation of thyroid activity to the production of gastric ulcer by bile salts 710
Taylor, N. B. (Weld, Branion and Kay): A study of the action of irradiated ergosterol, and of its relationship to parathyroid function 330
Teel, H. M.: Basophilic adenoma of the hypophysis with associated pluriglandular syndrome 585
Teitel-Bernard, A.: Action of insulin on the isolated mouse uterus..589
— (Parhon): Effect of insulin treated with acetyl on the volume of the spleen and on the arterial pressure in the dog...589
—— The mechanism of splenic contraction produced by insulin in dogs.....699
Tenery, W. C.: cf. Gammon.....215
Terplan, K. (Sanes): Pathological report of a case of Addison's disease treated with cortin..... 69
Tescher, G. L.: cf. Stanley.....153
Thannhauser, S. J.: Diabetic therapeutics 589
Thatcher, H. S.: cf. von Haam.....666
Thayer, A. (Levin and Doisy): Characterization of theelol.....576
Thayer, S. A.: cf. Doisy.....681
Thienes, C. H. (Hockett): Decreased absorption from the alimentary tract following injection of posterior pituitary extract.....213
Thies, O.: Iritis and menstruation. Considerations concerning the relation of endocrine secretions.... 91

Thivolle, L.: cf. Fontes.....333
Thomas, H. M.: The heart in hyperthyroidism 454
Thomas, P. C.: cf. Siegel 301
Thompson, K. W.: Technique for hypophysectomy of rat.....257
Thompson, Phebe K.: cf. Thompson 223, 710
Thompson, W. O.: Nervous manifestations of exophthalmic goiter at different stages of the disease....487
— (Thompson): Exophthalmic goiter. The development of refractoriness to iodine 223
— — Fallacies and dangers in the treatment of exophthalmic goiter by iodine 710
Thomson, J. S.: cf. Collip..... 86
Thorn, G. W.: cf. Hartman....155, 562
Toland, C. G.: cf. Askey.....103
Tonnet, J.: cf. Loeper.....334
Topper, A.: Basal metabolism in diabetic children 217
— The effect of thyroid extract on undernourished children 224
Tournade, A.: The central action of adrenin 677
— (Hermann and Malmejac): Secretion of adrenin following stimulation of the cranial and spinal meninges 565
— (Hermann and Jourdan): Curare and secretion of adrenin.....677
— (Malmejac): The vaso-sensory nerves and adrenin secretion..302
Trancu-Rainer, M.: Elimination of the sex hormones by the salivary glands 685
Trimble, H. C. (Carey): True sugar control of skin and of muscle in diabetic and non-diabetic persons.100
Tschernozatonskaia, E. P.: Further studies on erythrocyte sedimentation time in relation to function of thyroid gland 397
Tuttle, G. H.: The presence of a distinct insulin in depancreatized dogs 589
Turcu, T.: Agglutination of colon bacilli from goiter cases by serum from goiter patients 710
Turner, C. W. (Frank): The effect of the estrus producing hormone on the growth of the mammary gland 92
— — The relation between the estrus producing hormone and a corpus luteum extract on the growth of the mammary gland 92
— (Frank, Lomas and Nibler): A study of the estrus producing hormone in the urine of cattle during pregnancy 92
— (Gardner): The relation of the anterior pituitary hormones to the development and secretion of the mammary gland 446
Turner, C. W. (Schultze): A study of the causes of the normal development of the mammary glands of albino rat 443

Urmy, T. V. (Jones and Wood): A case of diabetes mellitus and fatty diarrhea due to carcinoma of the pancreas. Treatment with very high carbohydrate diet and insulin 449

Valenzuela, O.: Spontaneous hypoglycemia 699
Van Buskirk, F. W.: cf. Abbott....565
Van Caulaert, C. (Aron and Stahl): The presence of the hormone of the anterior lobe of the hypophysis which excites the secretion of the thyroid in the blood and cerebro spinal fluid, and its recovery from these fluids and from the urine 695
— cf. Aron 577
Van de Carr, F. R.: cf. Lyons.....574
Van Dyke, H. B.: cf. Gustavson....206
— cf. McIntyre 319
— cf. Wallen-Lawrence 324
Velhagen, K.: Pituitary (posterior lobe) extract and insulin.....213
Verbrycke, J. R., Jr.: Masked gastro-intestinal hyperthyroidism. Report of thirty-four cases 108
Verdier, H.: cf. Santenoise.....696
Veshnjakov, S.: cf. Lipschütz..... .....90, 573, 684
Victor, A. W.: cf. Koster.....562
Vidacovitch, M.: cf. Brieu.....696
— cf. Santenoise 696, 98
Vidgoff, B.: Posterior pituitary therapy in diabetes insipidus 289
du Vigneaud, V. (Fitch, Pekarek and Lockwood): Inactivation of crystalline insulin by crysteine and glutathione 699
Villela, G. G. (Penna de Azevedo): Studies in the normal thyroid in Rio de Janeiro 711
Vinogradova, T.: cf. Zavadovsky..324
Vogt, M.: Physiological proof of sympathetic innervation of the pituitary gland 585
Vogt-Möller, P.: On the pathogenesis of exophthalmic goiter. Decrease in elimination or in destruction of thyroxin? 334
Von Monakow, P.: Anterior lobe of hypophysis and growth.....323
Vigor, W. N.: cf. Barlow.....447
Voss, H. E.: cf. Loewe.....684

Wada, M.: cf. Yen.....201
Wagschal, L.: The Golgi apparatus and its position in the case of experimentally produced overactivity of the thyroid.....711
Wahncau, E.: cf. Bertram.....587

Walinski, F.: Attempted treatment of psoriasis with "Prolan" (pituitary anterior lobe hormone).....323
Wallace, H. L.: Hyperthyroidism; a statistical presentation of its symptomatology 335
Wallen-Lawrence, A. (Van Dyke): The gonad-stimulating substances of the anterior lobe of the pituitary body and of pregnancy-urine.324
Waring, J. I.: Mongolism in one of twins 204
Warner, F. J.: Histopathology of experimental diabetes insipidus..695
Watrin, J. (Florentin): Concerning the cause of milk secretion 685
——The thyroid and the genital tract 711
—cf. Collin 566
Watrin, M. (Brabant): The biologic interpretation of the Zondek reaction 685
Watson, E. M.: The percentage of eosinophils in blood smears from insulin-treated diabetics.....100, 449
Webster, B.: Studies in the experimental production of simple goiter 617
—(Chesney): Studies in the etiology of simple goiter 107
Wechsler, I. S. (Savitsky): Hyperthyroidism associated with Parkinsonian syndrome 335
Weichert, C. K.: Effect of experimental hyperthyroidism on reproductive processes of female albino rats 108
Weiss, A. G. (Monguio and Bernard): Effect of parathyroidectomy on the blood calcium 591
Weld, C. B.: cf. Taylor.....330
Werner, A. A.: Syphilis of the pituitary gland producing acromegaly 586
Werner, C.: cf. Parhon.....595
Werner, G.: cf. Parhon...101, 223, 677
Weser, W.: The roentgenographic treatment of feeble-mindedness in children 679
White, M. R. (Severance): Comparison of pregnancy tests.....311
White, W. E.: cf. Smith.....576
Whitehead, R. W. (Huddleston): Diffusibility of "female sex hormone" into the spinal fluid and its relationship to the oxytocic activity of the spinal fluid 312
Wible, C. L.: The catamenia and oxygen consumption 312
Wiesbader, H.: cf. Eufinger.....206
Wiesner, B. P.: cf. Lambie.....318
Wilckens, E. A.: cf. Lipschütz.....684
Wilder, J.: Spontaneous hypophyseal hypoglycemia 446
Wilder, R. M. (Johnson): Experimental chronic hyperparathyroidism: Metabolic studies in man....102
Will, G.: The suprarenals and tissue residual nitrogen 565
Williams, J. B.: Diabetic pyorrhea.327
Williams, J. R.: Extensive atrophy of subcutaneous fat following the repeated injections of insulin.....589
—The insulin coefficient, an improved method for the clinical control of diabetes mellitus....450
Williams, W. L.: cf. Burch.....578
Williamson, J. E.: cf. Collip..... 86
Willius, F. A.: cf. Pemberton.....709
Wilson, I. H.: cf. McClendon..... 89
Wilson, K. M. (Corner): The results of the rabbits ovulation test in the diagnosis of pregnancy....576
Wishnofsky, M. (Byron): The respiratory quotient. Its use in the diagnosis of diabetes mellitus....100
Wislicki, L.: Action of thyroid on spleen and blood volume 454
Wohl, M. G.: Diabetes mellitus and the gastric secretion 700
Wolfe, J. M. (Cleveland): Comparison of the capacity of anterior hypophyseal tissue of mature and immature female rabbits to induce ovulation 696
—cf. Burch 541, 578
—cf. Cleveland 579
Womack, E. B. (Koch): Studies on extraction of testicular hormone from tissues and on its quantitative distribution therein 267
——Testicular hormone content of human urine 273
Womack, N. A. (Gnagi and Graham): Adenoma of the islands of Langerhans with hypoglycemia: Successful operative removal.....218
—cf. Cole 335
Wood, Josephine, C.: cf. Urmy....449
Wortis, S. B.: cf. Coombs.....560
Wright, I. S.: Hereditary and familial diabetes mellitus 100
Wyalkova, P. A.: cf. Danilevskii... 98
Wyman, L. C. (Lutz): The effect of adrenalin on the blood pressure of the elasmobranch, squalus acanthias 677
—(Suden): Vascular responses to histamine in suprarenalectomized rats 81

Yater, M.: The tachycardia, time factor, survival period and seat of action of thyroxine in the perfused hearts of thyroxinized rabbits 224

Yen, T. J. (Kaiwa and Wada): Influence of the piqûre of Cl. Bernard upon the epinephrine discharge, the blood sugar content and the blood pressure 201
Yriart, M.: Sugar formation from phosphatids 218
— Thyroidectomy and pancreatic diabetes 224

Zaharescu-Karaman, N. (Nastase): The genital crisis of the new-born produced by the ovarian sex hormone 443
Zaleski, W.: cf. Buccheim.....440
Zavadovsky, B. (Vinogradova and Sarafanov): Contributions to the comparative physiology of the frontal lobe of the hypophysis....324
Zeckwer, I. T.: Spontaneous insulin resistance in rabbits. The effect of thyroidectomy on the response to insulin 101
Zerfas, L. G. (Koehler): Response of the reticulocytes in the treatment of two patients with pernicious anemia fed organic material obtained from the suprarenal cortex 82
Ziegler, K.: Bilateral ovarian changes in unilateral injury .....
Zondek, B. (Berblinger): Influence of female sex hormone and of hormones of anterior lobe of hypophysis on hypophysis of rats...586
Zunz, E.: The anti-diuretic action of extracts of the posterior lobe of the hypophysis 324
— (La Barre): Does the exocrine activity of the pancreas influence the secretion on insulin?..101
— — Is the increase in insulin which follows injections with adrenalin of pancreatic origin? 570

Subjects

Abderhalden reaction and hypophysis and ovarian extract 93
Acromegaly and diabetes.....318
——syphilis of hyophysis.....586
—serum of, and growth of young animals 212
Activity and testis hormone.....626
Addison's disease and cortical horhone of adrenal.....300
——cortin in..... 43
——metabolic studies in.....675
——pathology of..... 69
——roentgenographic study in.....559
——treated with adrenal cortex extract 285
—syndrome and granulomatosis....563
Adiposogenital dystrophy and diabetes mellitus.....444
Adrenal ablation and alimentary hyperglucemia 201
————blood constituents of rabbits 200, 203
————blood pressure following peripheral splanchnic nerve stimulation 299
————coagulation time of blood...439
————histamine poisoning, effect of injections of cortin on.. 80
————hypersensitiveness to intoxication 200
————hypoglycaemic action of insulin 588
————muscular fatigue 562
————susceptibility to toxins.....439
————tumor growth.....676
————vascular response to histamine 81
————vital hormone of adrenal cortex 79
——bilateral, and effects of absinthe 560
——in marsupial hibernation.....437
—— in rats and effect of cortin injection on resistance to toxins 79
————————substance in urine of normal human adults 80
—abscess and medullary reaction in cortical substance.....675
—adrenalin content of.....439
—and death from extensive superficial burns.....297
——erythrocyte volume 666
——estrin administration.....203
——eye disease.....568
——hypertension 20
——hypoglycemia 29
——immunological studies..... 78
——pregnancy 676
——red blood cells.....297
——tissue residual nitrogen.....565
—cortex and cholesterol metabolism 300
————hypophysis ablation in rat..322
————sex organ relationship.....300
——chief function of.....633
Adrenal cortex extract and development of testes 199
————malignant disease.....559
————————tumors 298
————————survival of decapsulated guinea pigs.....300, 438
————————toxins 562
————function of.....521
——hormone 77
————and Addison's disease.....300
————————Paget's Disease of the bones 109
————in Addison's disease.....675
————new method for separation of adrenalin from..... 81
——nature and structure of.....563
——studies 564
——substance and pernicious anemia 82
——treatment in vomiting of pregnancy 434
——vital hormone of.....79, 562
—(cortical) extract and precocious sexual maturity.....560
————effect of, on ovary.....639
————oral administration of.....560
——obesity, operative treatment of.562
—determination of area for irradiation of.....299
—distribution of lipoidal phosphorus in 676
—effect of follicular hormone on....302
————hypoglycemia on cellular activity of.....566
————removal of, on blood sugar after lumbar sympathectomy 567
—exhaustion, experimental..... 78
—extract, action of, on local immunization 677
————————red blood cells.....299
————————cellular metabolism....562
————————cerebral circulation....201
——and acetyl-choline..... 98
————amino acid increase in blood.675
————blood and organ lipoids.....200
————————fat 302
————————pressure 677
————cancer 201
————cardiac muscle.....199
————catatonia 440
————circulation 437
————cocaine sensitization 201
————glycogen distribution.....567
————growth in tadpole..... 82
————hexose-phosphate content of muscle 561
————hypersensitiveness to intoxication 200
————hypophysis 691
————insulin 85
————————action of, under anaerobic conditions 566
——and insulin increase 570
————metabolism of rabbit.....202
————muscle glycogen.....199, 200
————————sugar 297
————myasthenia gravis.....204

Adrenal extract and phosphorus content in brain and spinal cord 677
———rate of isolated heart.....105
———small intestine.....302
———sugar content of cerebrospinal fluid 448
———thyroid respiration.....107
——blood sugar response to, after thyroid feeding.....565
——calorigenic action of, after liver ablation 560
——central action of.....677
——cromaffin reaction of.....298
——(cortin) and body temperature.298
———in Addison's disease..... 43
——effect of intravenous injections of, on heart.....563
———on blood cholesterin 303
————carbohydrate metabolism, basal metabolism and vascular system 297
————nictitating membrane ..679
————proliferative activity of cells of adrenal medulla 635
————spinal fluid pressure...676
——in experimental carcinoma and sarcoma of rats.....302
——influence of one stomach secretion 300
——in hepatic disease 203
——injection, chemical effects of..677
——insulin, and sympathetic nervous system..... 38
——nitrogenous metabolism and glycemia in hypophysectomized dogs.....199
——secretion and curare.....677
———stimulation of cranial and spinal meninges.....565
——successful use of.....285
—genital syndrome 564
—glands, calcification in tuberculosis of.....559
——tumors of 563
—glutathione in, during gestation... 77
—graft, effect of hypotension on secretion of.....437
—hemorrhage in meningococcic bacteremia 438
———new-born 165
—insufficiency and acute peritonitis 79
——during pregnancy and cortin..155
——etiology and clinical aspects of.675
—irradiation and glycemia.....676
—lipoids, properties of.....677
—medulla, effect of adrenal extract on proliferative activity of.....635
——secretions of.....437
—operation and recurrent hyperthyroidism 561
—pathology of, in Addison's disease. 69
—relation between cortical and medullary portion of, in mammals.299
—secretion and vasomotor nervous system 439
—studies on lipolytic power of.....439
—tissue extract of toad, effect of..560
—tumor and pseudohermaphroditism 675
Adrenal, vascularization of 437
—vein blood and blood sugar..... 77
Adrenin and ergotamine, effect of on blood cholesterine.....303
—content in suprarenals.....301
—like substance sympathol.....438
Amenorrhea and ovarian therapy.. 45
Anemia in myxoedema 533
Anterior hypophysis hormone and calcium content of serum of cattle. 87
———follicular constancy 90
———hyperplasia of endometrium 94
Anterior lobe extract and follicular rupture in rabbits 213
———metabolism 208
——hyperpituitarism, observations on 611
——of hypophysis and cancer of uterus 211
———luteinizing principle of... 96
——substance, follicle stimulating effect of..... 95
—pituitary deficiency in mouse.....213
——extracts and ovulation.....83, 308
———sterilization 90
———thyroid 313
——hormone and menstruation....212
———in pregnancy..... 96
———treatment of psoriasis....323
——like hormone of placenta..... 86
——lobe substance by mouth..... 96
——luteinizing hormone.....321
———substance and uterine bleeding 319
——powder and ovary.....212
——sex hormone..... 96
——specificity in action of.....129
Aschheim-Zondek pregnancy test.. .....93, 304
—reaction, follicular hemorrhage in 93
———new method for.....578
——test 680

Basal metabolic rate and thyroid medication 455
———low, in asthenics.....704
—metabolism and adrenal extract..297
———diathermic treatment of testes 442
———hypophysis ablation.....686
———extracts 208
———oestrous cycle 208
———ovarian hormone 89
———posterior lobe.....315
————pituitary extracts.....210
——in diabetic children.....217
———dogs 569
———normal infants.....568
———rats in late pregnancy.....310
Basedow's disease and tetany.....369
——clinical anatomical biological parallels in.....332
——Golgi-apparatus in thyroid cells in 709
——Iodine metabolism in.....221
——treated with myxedematous thyroid gland.....452
Blood calcium and parathyroid ablation 591

Blood calcium and vitamin D after parathyroid ablation 450
— picture in goitre.....593
— pressure and goiter.....103
— sugar and adrenal vein blood..... 77
— — — castration 207
— — — posterior lobe extract.....689
— — changes under various experimental conditions.....324
— — content and piqûre of Cl. Bernard 201
— — effect of castration and thyroid ablation on.....223
— — — — injections of trypsin on...587
— — response to epinephrin after thyroid feeding.....565
Bone formation and parathyroid extract 547

Calcium and endemic goiter.....103
— in relation to cataract.....328
— metabolism and pancreas.....696
— — — parathyroid gland.....700
Cancer, effect of adrenal cortex and testis extracts on 302
Carbohydrate metabolism and adrenal extract.....297
— — in mongolian idiots.....84, 204
— — studies in.....216
Cardic vascular system in goiter....104
Carotid body, classed as paraganglion? 300
Castration and blood sugar.....207, 223
— — action of hypophysis.....315
— — composition and properties of milk from cows.....442
— — hyperfeminization in male rabbits 308
— — hypophysis implantation.....690
— — involution of thymus.....701
— — moulting in ducks.....304
— effect of, on anterior lobe.....445
— — — — scent glands of goat.....571
— — — thyroid extract on alimentary lipemia after.....333
— unilateral, and compensatory hypertrophy of remaining testicle.440
Catamenia and oxygen consumption.312
Cholesterol metabolism and adrenal cortex 300
Climacteric and intersexualities.... 89
Climate and metabolic diseases.... 52
Corpus luteum, action of folliculin on 572
— — and oestrin excretion.....310
— — — ovulation 88
— — — uterine activity.....193
— — effect of "gravidin" on.....571
— — extract and mammary gland growth 92, 443
— — — — oestrin, effect of, on uterus 441
— — — — ovary ablation in.....278
— — — effect of, on genital tract of normal and castrated female 573
— — formation and hypophysectomy 576
— — hormone and hypophysis.....691
— — implantation and oestrus..... 83
— — in a case of diabetes insipidus.326
Cortin in Addison's disease.....285
— — adrenal insufficiency of pregnancy 155
Creatinuria in hyperthyroidism.....104
Cryptorchidism, experimental in immature guinea pigs 306

Diabetes, a study of 500 cases.....100
— after hypophysectomy and pancreatectomy 326
— and acromegaly.....318
— — hypophysis ablation.....317
— — psychiatric reactions.....325
— — pyorrhea 327
— — sugar formation from phosphatids 218
— — thyroid ablation.....224
— association of vagotonic pancreatic extract with insulin in.....698
— effect of ingestion of burdock root in 449
— glucose-lactic acid cycle in.....216
— in children and basal metabolism.217
— influence of climate on..... 52
— — and pars tuberalis.....242
— — — sugar metabolism disorders.678
— — corpus luteum extract in.....326
— — histopathology of.....695
— — posterior pituitary therapy in..289
— — snuff-powder therapy with various posterior pituitary preparations 322
— in the negro race.....216
— insulin treated, and eosinophile..100
— mellitus after acute pancreatic disease 214
— — an analysis of 827 cases..... 99
— — and acute febrile diseases..... 99
— — — anterior lobe hormone.....690
— — — carcinoma of pancreas.....449
— — — experimental hyperinsulinism 29
— — — gastric secretion.....700
— — — hypophyseal obesity.....444
— — — pernicious anemia.....699
— — — pregnancy 698
— — — pulmonary tuberculosis.....588
— — — respiratory quotient.....100
— — — sugar consumption..... 99
— — — sympathetic system.....678
— — effect of sucrose and invert sugar injections in.....326
— — — hereditary and familial.....100
— — improved method for clinical control of.....450
— — insipidus, combined case of...447
— — metabolic-physiological theory of 215
— — with resistance to insulin....697
— (pancreatic) and hypophysis ablation 95, 678
— relation between sugar and glutathione in.....587
— sugar control of skin and of muscle in 100
— with insulin resistance.....699
Diabetic resistance to insulin treatment 216
— therapeutics 589
Diabetics, insulin treated and eosinophilia 449
Diuretic hormone of the brain....320

Dwarfism and infantilism.....687
Dysinsulinism, case report of..... 29
Dysmenorrhea and ovarian therapy. 45

Endocrine activity of ovary.....570
— articles on vitamin problems....296
— aspect of cutaneous diseases....678
— balance and coxa vara.....565
— coördination in amphibian color change 445
— disorders and industrial medicine.567
— dysfunction in mongolian idiots 84, 204
— function of ovarian homoio-grafts.205
— — — salivary glands.....566
— glands and bone metabolism.....109
— — — eye diseases.....568
— — — folliculine 568
— — — immunity 569
— — diseases and cholesteremia....593
— — effect of excessive ultra-violet irradiation on.....567
— — interrelationship of..... 83
— — — — hormones of..... 85
— organs, studies on conditions of activity in.....437, 439
— secretions and eye disturbances.. 91
— therapy, critique of.....597
— — in Lawrence-Moon-Biedl syndrome 337
— treatment of Paget's Disease....109
Endocrinopathies and mental retardation 679
Endometrial hyperplasia, experiments on.....541
Epinephrine and changes in liver glycogen and blood lactic acid....199
— discharge and piqûe of Cl. Bernard 201
Ergotamine, adrenin and, effect on blood cholesterine.....303
Estrin effect of, on growth and reproduction 684
— — — — reproduction system.....203
— hypophyseal antagonism.....647
— in urine as index of therapy in menstrual dysfunction.....361
Estrus producing hormone and mammary gland growth..... 92
— — — corpus luteum extract and mammary gland growth... 92
— — — in urine of pregnant cows.. 92
Exophthalmic goiter and iodine in blood 704
— — — — treatment 710
— — — periodic paralysis.....407
— — — refractoriness to iodine.....223
— — — renal function.....251
— — — tetany 369
— — cause of.....454
— — diagnostic significance of lymphoid tissue in 264
— — gastric secretion in.....707
— — in children.....221
— — influence of climate on..... 52
— — iodin, ethyl iodid and potassium iodid in.....104
— — irradiation of thyroid in.....702
— — nervous manifestations of.....487
— — pathogenesis of.....334
— — quinine and iodine in.....157
Exophthalmic goiter, study of incidence of 106
— — treated with physostigmine....221

Fat metabolism and insulin..... 98
Female and male sex hormone, coexistence of.....684
— sex hormone.....571, 572
— — — diffusibility of.....312
— — — in blood of carcinomatous male patients.....681
— — — influence of.....586
— — — injections and pregnancy in guinea pig..... 88
— — — terminology of.....573
Follicle-stimulating hormone and menstrual dysfunction.....361
Follicular and luteal hormones, antagonism of..... 86
— extracts, influence of, on endocrine system 566
— hormone absorbed through mucous membrane of gastro-intestinal tract 309
— — from urine of pregnant women.310
— — gastric absorption of.....207
— — in crystalline form.....307
— — — urine as index of therapy in menopause 366
— — peroral effect of.....684
— — physical and chemical properties of.....571
— — study of..... 90
Folliculin, action of, on oviduct of turtle 441
— and auto grafts of vaginal mucosa 207
— — uterine changes 304
— biological estimation of.....684
— effect of, on arterial pressure....681
— — — — blood cholesterin.....303

Gigantism, report of a case....120, 611
Glandular dysfunction and obesity.. 82
Glucose formation from lactic acid in liver 99
Glycopenia, causes of.....182
Goiter and blood pressure.....103
— blood picture in.....593
— cardiac features of.....709
— (endemic) and iodine content of food, water, air and soil.....707
— — — — deficiency 103
— etiology of.....107
— treated with physostigmine 221
— evidence of bacterial factor in...710
— experimental production of.....617
— focal cyclic growth as factor in production of 594
— in children 221
— iodine deficiency theory of.....705
— pathogenesis of.....594
— pathological classification of.....453
— prevention in Detroit and Cleveland 594
— production and thymus extirpation 331
— site of action of iodine in..... 65
— study of etiology of.....333
— toxic, and heart block.....592
— — radium and roentgen rays treatment of 709

Goiter, treatment of 592
Gonad ablation and liver-glycogen..205
— and hypophysis.....210
— — — reciprocal action of.....683
— — — relation between.....690
— horomone functions.....574
— relation of adrenal cortex to.....521
— stimulating complex of anterior pituitary, oestrin effect on.....655
— — hormone in urine of pregnancy.205
— — substance of pregnancy urine and reproductive tract of male 538
— stimulation and hypophysis implantation 207
Graafian follicles, influence of folliculin on 304
Graves' disease, specific dynamic action in 706
Growth and thymus.....220
— — water-intake 83
— effect of estrin on.....684
— hormone and thyroid.....569
Gynecomastia and hypophysis..... 93

Hormone analysis of blood and urine of non-pregnant women after transfusion of blood from pregnant donors 87
Hyperadrenalism and primary hypertension in childhood.....301
Hyperglycemia and posterior lobe extracts 313
Hyperglycemic action of blood of diabetic dog 99
Hyperinsulinemia, clinical course of.325
Hyperinsulinism and epileptoid attacks 293
— — glycophenia 182
— — hypoglycemia 215
— case reports of..... 29
Hyperparathyroidism and bone lesions 590
— — similar diseases of bone.....222
— experimental 102
— with hypercalcaemia and decalcification of bones.....101
— — osteitis fibrosa cystica 101
Hyperpituitarism beginning in infancy 120
Hypertension and adrenals..... 20
Hyperthyreosis, dietetic treatment of 334
Hyperthyroidism and adrenal ablation 561
— — creatinuria 104
— — diiodotyrosine 220
— — fat tolerance 596
— — gastro-intestinal disturbances..108
— — ketonuria 702
— — Parkinsonian syndrome.....335
— — quinine 157
— — tetany 369
— cardiac output in.....452
— effect of, on heart.....454
— experimental, and brain phosphorus 223
— — — reproduction 108
— — tachycardia 223
— in animals and calcium and water content of cardiac muscle.....453
Hyperthyroidism in 10-year-old child.103
— native complement in.....105
— radium and roentgen rays treatment of.....709
— statistically presented symptoms of 335
— treatment of.....222
Hypoglycemia and oral administration of insulin.....217
— causes of.....182
— due to hyperinsulinism.....215
— high fat diets in treatment of....182
Hypophyseal cachexia, cases of..... 95
— infantilism, case of.....445
— ovarian relationship.....578
Hypophysis ablation, action of phloridzin after.....315
— — and action of phlorizin.....209
— — — adrenal cortical extract.....639
— — — — extract 199
— — — basal metabolism.....686
— — — blood iodine.....690
— — — body temperature.....585
— — — calcium and phosphorus in plasma 210
— — — C/N ratio.....314
— — — hemoglobin 212
— — — influence of bacillus coli vaccine on nitrogen metabolism 209
— — — nitrogen metabolism and sugar in fasting.....578
— — — — output 578
— — — nitrogenous metabolism 209
— — — pancreatic diabetes..... .....95, 211, 326, 678
— — — phlorizine diabetes.....317
— — — phosphate and phenol excretion 316
— — — Prolan administration.....445
— — — protein minimum.....209
— — — replacement therapy.....322
— — — specific dynamic action.....210
— — effect of, on ovulation and corpus luteum formation.....576
— — — — — reproductive system...578
— — fasting and protein metabolism 208
— — hypoglycemic action of blood after 687
— — technique for in rat.....257
— action, of hypertensive and ocytocic principles of posterior lobe of, and basal metabolism.....315
— — — on sex glands of fish and reptiles 581
— and amphibian color change.....445
— — Bidder's organ.....211, 582
— — brain, functional relations of..242
— — castration 315
— — diabetes insipidus 678
— — estrin administration.....203
— — eye disease 568
— — gigantism 120
— — gonads, reciprocal action of.. .....574, 683
— — — relationship 210
— — gynecomostia 93
— — juvenile obesity.....601

Hypophysis and ovulation in the hen.583
——pseudo-pregnancy 315
——sex 319
——sugar metabolism.....446
——thyroid disturbances..... 83
— (anterior lobe), action of.....691
————respiratory exchange.....443
————on ovary.....577
———activity and thyroid.....312
———and gonads 690
————ovary transplants.....689
————placenta 584
————thyroid 565
———differential stain for.....579
———effect of castration, grafts and implantation of gonads on 445
———effects of folliculin.....568
————oestrin on.....655
———extracts, action of, on immature testes.....506
———and chemistry of liver.....444
————growth 323
————mammary gland development 443
————oestrous 686
————ovary stimulating hormone 443
————reproductive ability of rat 582
————testes 513
————thyroid 686
————thyroid activity.....331
————condition of pigeons.567
————transplantation 706
———effect of, on growth and fat accumulation.....694
————laboratory and domestic animals.316
————thyroid 584
————in Simmond's disease....686
————oral administration of....691
————pharmacological method for the evaluation of action of 318
———hormones and clinical syndromes 318
————diabetes mellitus.....690
————growth 686
————hyperplasia of endometrium 581
————leucocyte counts.....585
————male gonad.....314
————mammary gland secretion 446
————menformon 318
————parabioses 690
————pregnancy reaction in male mice.....316
————prolan 444
————secretion of crop gland in pigeons...321
————thyroid 569, 577
————secretion in blood and cerebrospinal fluid 695
————effect of, on gonads, of pigeon 446
————growth and puberty 691
Hypophysis, anterior lobe hormones from urine of pregnancy 694
————in cerebrospinal fluid during pregnancy 695
————influence of.....586
————on ovary and thyroid 685
————testicles of guinea pigs 579
———implants and senile ovaries of mice.....445
———method for diagnosing over- and under-activity of.....443
———powdered, properties and durability of.....582
———sex hormone in pubertas praecox 529
————sex stimulating hormone of 694
———silver impregnation of capillary endothelium of.....318
— anti-diuretic principle and epilepsy 693
— basophilic adenoma of.....585
— cerebri, centers of.....692
——squamous epithelial rests in...314
— comparative physiology of frontal lobe of.....324
— control of cutaneous pigmentation in an elasmobranch fish.....691
— dysfunction and behavior problems 303
— effect of follicular hormone on...302
———hypoglycemia on cellular activity of.....566
———thyroid ablation on structure of 439
— essential nature of.....691
— experimental embryology of.....443
— extract, action of, on ventricle...687
——and Abderhalden reaction..... 93
———carbohydrate reserves.....313
———catatonia 440
———glycogen distribution 567
————lactation 304
———metabolism of rabbit.....202
———specific dynamic action of proteins 316
———water exchange.....212
——effect of, on intestinal peristalsis 580
————tonus of human pelvis.444
——in treatment of hypopituitarism 582
——pressor and melanophore principle of 95
— fibroma of 584
— finer structure of cells of.....687
— function in toad.....689
— gonad ovulation mechanism in adult amphibians 443
——stimulating substance of anterior lobe of.....324
— growth of anterior lobe of..... 1
— homo-implants and reproductive tract of the male.....583
— hormones and male reproductive system 97
——of, and lactation..... 84

Hypophysis, hormones of anterior lobe of 315
——(prolan) and male gonad.....319
——sex action of, on male animals.318
——test of.....693
—implantation and gonad stimulation 207
————ovary grafts.....211
————puberty 690
————sex glands.....690
—implants, effect of, on ovaries....210
—in Addison's disease..... 69
—influence of seminal epithelium on 309
—injury and diabetes mellitus.....447
—lesion of, and dwarfism.....687
—like substance in urine of carcinomatous women.....689
—of an orang-utang.....321
—ovary antagonism.....647
—physiologic proof of sympathetic innervation of.....585
—(posterior lobe) and melanophore hormone 688
————extract and blood pressure..689
——————changes in liver and kidneys 580
——————diuresis 524
——————hyperglycemia 313
——————insulin 213
——————pilocarpine 580
——————coagulation properties of.445
——————effect of, on lactic acid of blood 583
——————when introduced into cerebral ventricles 579
————hormone and nephropathy and eclampsia in pregnancy 576
————hormone, antidiuretic component of 317
————substance of, and blood coagulation 319
——————of and fat in blood.....212
—regulated by testes.....583, 693
—sex hormone of, and ovary graft..206
—sexual hormone of.....580
—silver impregnation method in studying 212
—structure and development of pars tuberalis of.....320
——of cells of.....687
—syphilis of, and acromegaly.....586
—therapy in alopecia.....313
—tissue, age changes in secretion..696
Hypopituitarism, juvenile, and growth hormone 1
—with glandular treatment.....582
Hypopituitary disease with hemiplegia, hypertension and sugar tolerance curve.....585
Hypothyroidism, symptomatology of.223
Hysterectomy and voluntary activity in rat 86

Insulin action following adrenal ablation 588
——of, on blood cholesterin in nephritis 588
————intraocular pressure.....698
————isolated mouse uterus....589
Insulin, action on frogs 447
————muscle contraction 214
————perfused frog heart and isolated rabbit intestines ...214
————trypsin injections 587
—and acetyl-choline 98
——adrenal extract, action of under anaerobic conditions....566
——blood fat 302
——catatonia 440
——changes in liver glycogen and blood lactic acid 199
——eosinophils 100
——metabolism 98
——gastric secretion 217, 300
——gastroduodenal troubles 697
——glucose, effect of, on normal and obstructed intestine 588
——————serum calcium 98
——glycogen distribution 567
————in liver 587
——heart rate after sympathetic and vagus ablation 447
——hexosephosphate of muscle....561
——hypoglycemia 217
——liver extract 587
————glycogen 696
——muscle glycogen 199
——posterior lobe extract 213
——sex cycle in white rats 214
——small intestine 302
——spleen contraction 697
——splenic contraction 699
——sterilization 90
——sugar content of cerebrospinal fluid 448
——sympathetic ablation 215
——thermoregulation 216
——thyroid ablation 101
————action 453
————respiration 107
——vagotonia 448
——vagotonic pancreatic extract in diabetes 698
——variations in liver and muscle glycogen after pancreas ablation 326
—administration and glycogen variation in liver and muscles 326
—a specific antigen 587
—allergy 417
—angina 217
—coefficient and clinical control of diabetes mellitus.....450
—(crystalline), inactivation of.....699
—diabetic resistance to 216
—effect of, on blood cholesterin...303
————ovary 309
————sympathetic nervous system 98
——on thyroid 453
—enteral administration of.....696
—free pancreatic extracts 447
—hypoglycemia, variations in gastric secretion during 697
—increase following adrenal extract 570
—in depancreatized dogs 589
—injections and atrophy of subcutaneous fat 589

Insulin in malnutrition 448
— overdosage, observations on complex symptoms which accompany 326
— oversecretion, case of 699
— physiological studies on..... 99
— secretion and exocrine activity of pancreas 101
— — — intra- and extra-pancreatic hyperglycemia 697
— — reduction of, during excessive external secretion of pancreas 588
— sensitivity of non-diabetic humans 217
— treated with acetyl, effect of, on volume of spleen and arterial pressure 589
Insulinemia in obesity and in emaciation 215
Internal secretions and myasthenia gravis 204
Intersexualities at puberty and climacteric 89
Iodine and quinine in exophthalmic goiter 157
— content of air, soil, water and food in region of endemic goiter 707
— — — blood 704
— deficiency, effects of, on thyroid and parathyroid glands 146
— — theory of goiter 705
— metabolism and thyroid extract..704
Islands of Langerhans, adenoma of.218
— — — and hyperinsulinism 29
— — — circulation in 587

Lactation and hypophysis extract..304
Lawrence-Biedl syndrome 693, 695
— — — case report of..... 97
— — — pathogenesis and heredity of 583
Lawrence-Moon-Biedl syndrome 337
Liver, and lactic acid removal from blood 99
— — protein metabolism in the rat.. 97
— changes and posterior lobe extracts 580
— extract and insulin 587
— function and blood serum from patients with Graves' disease..264
— glycogen and insulin 587
— in treatment of diabetes mellitus.326

Male and female sex hormone, coexistence of 684
— — — — — — separation of.....205
— gonad and hypophysis hormone..319
— hormone, purification of 572
— — studies on 87
— reproductive system and hypophysis hormones..... 97
— serum, action of on combs of capons 91
— sex hormone in young woman suffering from virilism 309
— — — isolation of 87
Mammarian extracts, influence of, on endocrine system 566
Mammary glands, effect of hormones on 84
— — growth and estrus producing hormone 92
— — — corpus luteum extract and estrus producing hormone in 92
Menopause, joint affection during...308
— roentgen therapy in 682
— therapy in, and follicular hormone 366
Menorrhagia and ovarian therapy... 45
Menstrual cycle and uterine hemorrhage 306
— disturbances and injection of pregnancy blood 305
— — — oestrous hormone therapy..311
— dysfunction, and hormones in urine 361
Menstruation and anterior pituitary hormone 212
— — eye disturbances 91
— — — hyperinsulinism 29
— phylogeny of 573
Metabolic studies in man.....102
Metabolism and posterior pitiutary hormone 313
— observations in normal children..209
Metrorrhagia and diathermy of thyroid 595
Mineral metabolism and thyroid....369
Mongolism in one of twins.....204
Myxedema and pernicious anemia... .....105, 705
— and renal function 251
— case of 409
— clinical study of, in Michigan....595
— gastric secretion in 707
— treatment of anemia in.....533

Obesity and glandular dysfunction.. 82
— — optimal weight estimation....492
— — testis extract 153
— (juvenile) study of 601
— level of, oxygen exchange in.....592
Oestrin found in urine of pregnant cow 573
Oestrous and anterior lobe extract.686
— — uterine contraction 193
— cycle and basal metabolism 208
— — — parabiosis 307
— — — testis hormone 441
— hormone therapy 311
Osteitis fibrosa generalisata and parathyroid enlargement 327
Ovarian deficiency and ovary extract 88
— therapy and menstruation 45
Ovary ablation and corpus luteum extract 278
— — inhibition of neutral characters by heifer serum after 680
— activity and structure of uterine horn 682
— and anterior lobe of hypophysis.577
— — — — — substance 95
— — — pituitary powder.....212
— — hypophysis implants 210
— — — relationship of 578
— (bilateral) changes in unilateral injury 685

Ovary dysfunction and Roentgen ray treatment 572
— effect of adrenal cortical extract on 639
— — — hormone of, on plumage of bird 682
— — — insulin on 309
— — — substances of, on excised uterus 684
— — — thyroid implantation on....711
— endocrine activity of.....570
— extract and Abderhalden reaction 93
— — — growth in tadpole 82
— — — sugar metabolism 85
— — — uterine motility 193
— — in ovarian deficiency 88
— — — urine of pregnant cows.....684
— — use of, in gigantism 611
— graft in males 206
— grafts and hypophysis implantation 211
— — — parabiosis 684
— — — seminal vesicles 307
— — — sterilization 90
— — effect of, on anterior lobe.....445
— — endocrine function of.....205
— — in male and female mice.....681
— — — unspayed rats 440
— hormone, effect of, on gonad-stimulating complex of anterior pituitary 655
— — lack of, and joint affection....308
— — of, and lactation 84
— — — — metabolism 89
— — (theelol) 576
— hormones and hyperplasia of endometrium 94, 581
— hypophysis antagonism 647
— influence of anterior lobe hormone on 685
— — — on motility of non-gravid uterus 442
— irradiation, effect of, on pregnancy 575
— multiple transplants of, and oestrous cycle 307
— oxygen, use of 90
— preparations and specific dynamic action 316
— reactions of, to injections of placenta 683
— — — to testicular hormones 206
— sex hormone and genital crisis..443
Ovary stimulating hormone of hypophysis 443
— testicular tubular adenoma of....310
— therapeutic irradiation of.....575
— transplantation, experimental ...207
— — further observation on.....307
— — new experiments on 90
— transplants and hyperfeminization in male rabbit 308
— — — hypophysis 689
— tumor, transplantation of.....679
Ovogenesis and normal follicular cycle in adult mammalia 305
Ovulation, effect of hypophysis extract on 583, 696
— following parabiosis 582
Ovulation in pregnancy after injection of urine from pregnant women 309
— — rabbit 206
— mechanism of 88

Pancreas ablation and tryptophane in blood and tissues 204
— — insulin 326
— action of drugs on internal secretion of 325
— activity and insulin 101
— acute disease of, and diabetes mellitus 214
— and calcium metabolism 696
— — hypophysis ablation 678
— carcinoma of, and high carbohydrate diet 449
— circulatory hormone of 98
Pancreas, effect of hypoglycemia on cellular activity of 566
— extract and growth in tadpole... 82
— — insulin free 447
— hyperinsulinism and dysinsulinism 29
— in Addison's disease 69
— intense secretory activity in, on reduction of blood sugar by insulin 588
Pancreatic diabetes and hypophysis ablation 211
— hormone, dual nature of.....696
Parabiosis and anterior lobe hormone 690
— — oestrus cycle 307
— — ovarian grafts 684
— — precocious puberty 582
— — sex transformation 85
— experiments with 593
Parathormone (Collip's) and bone transparency 701
— — — calcium content of brain and kidney 219
Parathyroid ablation and blood calcium 591
— — — calcium in blood serum.....703
— — — phosphorous condition 101
— — — red cell sedimentation rate.703
— — — scleroderma 591
— — — vitamin D 450, 700
— — physiological diffusible calcium in serum after 703
— — use of irradiated ergosterol after 700
— and blood calcium following fluorine 222
— — dietary deficiency of iodin.....146
— — eye disease 568
— — osseous diseases 330
— — strontium poisoning 202
— deficiency, case history of.....358
— effect of hypoglycemia on cellular activity of 566
— enlargement and osteitis fibrosa generalisata 327
— extract and bone formation.....547
— — — metabolism of rabbit 202
— — — phosphorus of brain and spinal cord 595
— — — tetany 590

Parathyroid extract, cataract 328
——(Collip's) and blood calcium..595
——effect of, injected into cerebrospinal fluid 700
————on tonus and peristalsis in stomach and intestine 329
—function and irradiated ergosterol.330
—gland and calcium metabolism...700
—hormone and carcinoma 219
———and growth of rat carcinoma.701
———ossification 93
———Paget's disease 109
——chemistry and physiology of..218
—hyperplasia and osteitis fibrosa cystica 101, 701
—hypertrophy after denervation of carotid sinus and cardio aortic zone 327
—tetany, action of irradiated ergosterol on 591
——and irradiated ergosterol.....327
——contributory factors in 219
Parturition studies 310
Pernicious anemia and adrenal cortex substance 82
———myxedema 105
——influence of climate on..... 52
Physiology of exercise 569
Pituitary cachexia and somnolence.402
—(posterior) extract, water and halides in blood and urine 319
—therapy in diabetes insipidus....289
Placenta, action of hormones of.... 86
———injections of, on ovary.....683
—extracts and sterilization..... 90
——influence of, on genital tracts of young rats 303
—implantations and Aschheim-Zondek test 584
Posterior pituitary extract and alimentary tract absorption 213
————basal metabolism 210
——hormone in metabolism 313
Pregnancy and anterior pituitary hormone 96
——basal metabolism rates 310
——diabetes mellitus 698
——estrus producing hormone..... 92
——female sex hormone injections 88
——hypophysis hormone 695
——Reid Hunt reaction 206
——thyroid extract 107
——weight calculation 91
—Aschheim-Zondek test for 304
—blood of, and menstrual disturbances 305
—cortin in adrenal insufficiency during 155
—diagnosis by rabbit ovulation test.576
—effect of ovary irradiation on....575
———urine of, on genital tract of castrated male rats.....570
————————male and female hedge hog 683
—Golgi apparatus and vacuoles in adrenal in 676
—hormones and fetus growth.....207
—influence of, on thymus.....102
—iodine content of blood in.....450
Pregnancy, preparation of pure follicular hormone from urine of....571
—reaction in male mice following injection of urine containing sex hormone of hypophysis....316
—recent advances in Zondek-Aschheim test for 225
—response of uterus of cat.....206
—test 93, 572, 679
—tests, comparison of 311
—tetanoid syndrome in.....573
—thyroid function in 702
—urine, effect of injection of.....303
————on experimental cryptorchid testes 307
————————pregnant and non-pregnant cat 571
——extract of, and testes.....506, 513
——new extract from 681
——of, and changes in genital tract of kittens 570
———response of cryptorchid testes to 681
—vomiting of, and adrenal cortex extract 434
Progestin, rôle of, in female reproductive cycle 576
Prolan administration and hypophysis ablation 445
—and anterior lobe hormones.....444
Prostate, studies on causes of hypertrophy of 574
Protein metabolism in fasting hypophysectomized dogs 208
Pubertas praecox, case of.....529
Puberty and anterior lobe of hypophysis 90
——intersexualities 89

Reproductive and hypophysis ablation 578
—effect of estrin on 684
—in female albino rats and experimental hyperthyroidism 108
—physiology of, in birds 321, 446
Reproductive cycle, metabolism of women during 304
—organs and hypophysis ablation in rat 322
Respiratory quotient and diabetes mellitus 100

Seminal vesicle grafts in mice.....574
Sex and functional differences in hypophysis 319
—cycle and folliculin 304
——immunologic aspects of 574
——in birds, studies on..... 85
———rats, effect of insulin on....214
—glands and hypophysis implantation 690
———juvenile obesity 601
—hormone and ovary tumor.....679
———sympathetic nervous system.440
——antagonism 574
——chemical investigation of.....680
——elimination of, by salivary glands 685
——masculine, from urine and assay by comb method 307

Sex hormone of anterior pituitary.. 96
— organs and calcium content of serum of cattle 87
— — of guinea pigs, and anterior pituitary 129
— — relation of to adrenal cortex...300
— reversal 206
— transformation in parabiotic amblystoma 85
Sex, influence of ischemia on evolution of elements in.....679
— regulating hypophysis 583
— tissue and comb growth stimulating hormone 267
— transplantation of 682
Sexual hormone of hypophysis 580
— maturity and adrenal extract....559
Simmond's disease in childhood....694
— — necropsy findings in case of...323
— — treated with anterior lobe extract 686
— — cases of 95
Spleen, an endocrine organ.....701
— — organ of internal secretion ...591
Sterility and ovarian therapy..... 45
Sugar control of skin and of muscle in diabetics and non-diabetics....100
— metabolism and hypophysis 446
Sympathetic nervous system, effect of removal of on blood sugar.....567

Temperature and thermal reactions of hypophysectomized dogs 213
— action of extracts of anterior lobe and pregnancy urine on...506, 513
— — — urine of pregnancy on.....680
— and comb growth promoting substance 86
— — hypophysis 693
— development and adrenal cortex extract 199
— — — after injections of urine of pregnancy 680
— diathermy of, and basal metabolism 442
— extract and comb growth 303
— — — growth in tadpole..... 82
— — — weight 153
— — effect of on comb growth.....575
— — in experimental carcinoma and sarcoma of rats.....302
— — use of, in gigantism.....611
— hormone and oestrous cycle.....441
— — and spontaneous activity 626
— — — vitamin B deficiency 441
— — extraction, distribution and action of 441
— — reaction of ovary to 206
Testicle transplants, lasting effects of 683
Testicular grafts, effect of, on anterior lobe 445
— hormone content of human urine.273
— — extraction of, from tissues....267
Tetany and diffusible calcium of the blood stream 328
Thermal reactions and temperature of hypophysectomized dogs 213
Thymus and anterior lobe extract..584
— — estrin administration 203
Thymus and growth 220
— — Hassall's corpuscles 331
— — lymphatic system 701
— — thyroid antagonism 594
— effect of castration on involution of 701
— — — hypoglycemia on cellular activity of 566
— extirpation and goiter production.331
— extract, action of, on human pregnant uterus 102
— — in experimental carcinoma.....302
— gland and anterior pituitary hormone 83
— grafts 701
— influence of on skeleton formation 105
— — — pregnancy on 102
— — on growth 107
— origin of Hassall's corpuscles in.591
— pathology during inanition 85
— relation of, to other endocrine organs 591
Thyroid ablation and blood iodine..690
— — — elimination of urinary carbon and nitrogen 333
— — — iodine metabolism 221
— — — insulin 101
— — — pancreatic diabetes 224
— — — structure of hypophysis 439
— — — triptophane in blood and tissues 204
— action of, on moulting and feather structure 595
— — on spleen and blood volume...454
— activity and gastric ulcer 710
— administration and anorexia.....706
— — — obesity 592
— and anterior lobe activity.....312
— — — — extract 584, 686
— — — — hormone 569
— — — pituitary extract 313
— — cardiovascular system 104
— — dietary deficiency of iodin.....146
— — erthyrocyte sedimentation time.397
— — estrin administration 203
— — eye disease 568
— — hypophysis 565, 577
— — — ablation in rat 322
— — — (anterior lobe) extracts....567
— — — disturbances 83
— — insulin 453
— — nystagmus 431
— — specificity in action of anterior pituitary 129
— — tissue fluid, relation between..106
— — thymus antagonism 594
— bud, transplantation of.....592
— cells, Golgi apparatus in, in Basedow's disease 709
— changes according to age.....331
— color reaction of colloid in.....593
— cystological studies on.....332
— denervated 705
— diathermy and metrorrhagia 595
— disease and cholesteremia 593
— disturbances and ocular changes.452
— effect of certain therapeutic measures on protein equilibrium ...334
— — — follicular hormone on.....302

Thyroid, effect of hypoglycemia on cellular activity of 566
— extract, action of, on bile secretion 596
— — administration and iodine metabolism 704
— — and catatonia 440
— — — diazo-reaction 222
— — — diuresis 452
— — — gastric acidity 221
— — — glycogen content of heart..451
— — — — distribution 567
— — — growth in tadpole..... 82
— — — metabolism of rabbit.....202
— — — myasthenia gravis 204
— — — phosphorus of brain and spinal cord 595
— — — pregnancy 107
— — — rate of isolated heart 105
— — — sodium chloride equilibrium of the blood 451
— — — specific dynamic action of sugar 332
— — (synthetic), action of 705
— — and tetany 590
— — — thyroid respiration 107
— — dependence of, on nutrition...594
— — effect of, on alimentary lipemia of dogs 333
— — — on undernourished children.224
— — place and manner of action of.708
— — seat of action of, in perfused hearts of thyroxinized rabbits 224
— — studies on 450
— — synthetic, effect of, on urinary carbon and nitrogen 333
— feeding and blood change 707
— — blood sugar response to epinephrin after 565
— function and cervical sympathetic removal 331
— — — Reid Hunt reaction 453
— — — stimulation of cervical sympathetic 332
— — in pregnancy 702
— gland and iodine metabolism in pregnancy 450
— — colloid release from follicle cell 103
— — production of hyperplasia of, by chemical means 335
Thyroid hormone in blood and urine.264
— hormone in blood and urine.....264
— — in blood of pregnant women.. ..... 220, 706
— — — mother's milk 222
— implantation, effect of, on ovary.711
— influence of anterior lobe hormone on 685
— — — on edema 705
— — — — skeleton formation 105
— — — upon poisonous action of various drugs 334
— — on growth 107
— in fowls, factors affecting size and iodine content of 451
— iodine deficiency and 103
— irradiation in exophthalmic goiter.702
— lateral aberrant 451
— malignancy, clinical aspects of...451
Thyroid medication and blood picture 455
— normal, and iodine 65
— overactivity and Golgi apparatus.711
— — — with normal metabolism in early phase 703
— overfeeding in chickens 596
— papilliferous tumors of 708
— parathyroid system and blood serum calcium 709
— parenchyma, experimental regeneration of 705
— pathology during inanition 85
— — in new born 331
— — of, in Addison's disease..... 69
— patients, value of cholesterol determination in 704
— persistence of embryonic structure in 452
— preparations and feather germ indicator 333
— psychosis, diagnosis of 453
— second epithelial component of..708
— secretion and anterior lobe hormone 695
— studies on normal 711
— transplantation in guinea pig....706
— quinine and iodine in disorders of.157
— relation of, to spleen.....454
— respiration of 107
— secretion and quinine 592
— substance and creatinine content of liver and muscles 220
— therapy and menstruation 45
— treatment and anemia of myxoedema 533
Thyroiditis, chronic 705
Thyroparathyroid ablation and blood sugar 223
— — — — — cardiac-moderation 450
— — — — phosphorous condition 101
Thyrotoxic circulatory symptoms with low metabolic rate 595
— state, method of estimating 331
Thyrotoxicosis, recurrent cases of..592
Thyroxin, synthetic, action of on chronaxie 333

Urine, effect of injection of on genital organs 303
Uterus and milk secretion 685
— — pregnancy response 206
Uterus, cancer of, and anterior lobe of hypophysis 211
— effect of corpus luteum extract and oestrin on 441
— fibroma of 584
— hemorrhage, studies on 306
— morphological study of horns of, during sexual repose 682
— motility of, and ovary extract...193
— studies on 442

Vagus substance in blood.....202
Voluntary activity and hysterectomy 86
Virilism in young woman.....309

Water-intake and growth 83

Zondek-Aschheim pregnancy test, recent advances in 225
Zondek reaction, biologic interpretation of 685